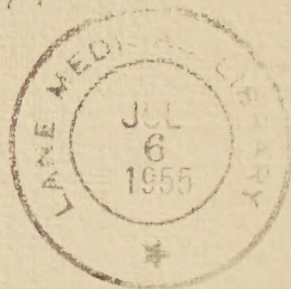


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STUDIES ON RADIOIODINE TREATMENT OF THYROTOXICOSIS

WITH SPECIAL REFERENCE TO THE BEHAVIOUR
OF THE RADIOIODINE TRACER TESTS

BY

LARS-GUNNAR LARSSON

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Contents

	Page
Preface	5
Introduction	7
Chapter I. Some Comments on the Tracer Tests with Radioactive Iodine	9
1. The Iodine Metabolism: A Brief Review	9
2. Tests Based on the Accumulation of I^{131} in the Thyroid	11
3. Tests on the Release of Organic I^{131} from the Thyroid	32
4. General Scheme of the Investigation	35
Chapter II. Composition of the Series and Therapeutic Results	37
1. Introduction	37
2. Factors of Importance to the Result	37
3. Practical Management of the Treatment	41
4. Composition of the Series	45
5. Results of Treatment	54
6. Disadvantages and Complications of Treatment	79
Chapter III. Behaviour of the Tracer Tests after the Treatment	91
1. General Considerations	91
2. The Accumulation of I^{131} in the Thyroid	94
3. Prognostic Importance of Early Tracer Tests	114
4. The Organic Binding of I^{131} in the Gland	123
5. The Release of Organic I^{131} from the Gland	136
Summary	141

Preface

The present investigation was conducted at Radiumhemmet from 1951 to 1955. It was started under my former chief, the late Professor Hugo Ahlbom, whose great kindness and interest meant so much to me during the first period.

Ty my present chief, Professor Sven Hultberg, I am greatly indebted for all his help, interest and encouragement and for the way he facilitated this work in the Clinic.

Essential for this investigation was the availability of a clinical series and the close collaboration of colleagues with wide experience of the management of hyperthyroidism. Dr. Hjalmar Wijnbladh selected from his series of toxic goiters at St. Göran's Hospital more than half the cases in the present series for radioiodine treatment. His careful selection, detailed clinical analysis and management of the patients before and after radioiodine treatment, as well as his advice on re-treatment, were of fundamental importance for this investigation.

For the same reasons I want to express my warm thanks to Dr. Rune Frisk, who started the collaboration with Radiumhemmet in this field and whose long experience with the medical treatment of hyperthyroidism was of the utmost value for the work.

I am also greatly obligated to many other colleagues at medical and surgical services in Stockholm and the provinces for valuable clinical collaboration. To my colleagues at the Medical Clinic of Karolinska Sjukhuset I am indebted especially for indispensable help with patients hospitalized at Radiumhemmet during the treatment, many of whom presented difficult medical problems.

To Dr. G. Widström I am exceedingly grateful for the estimations of protein-bound serum iodine, which otherwise would not have been possible to carry out in this series.

Also essential for this investigation was access to technical resources and a laboratory of work with radioactive isotopes. Besides my aforementioned chiefs, my acknowledgments are due, in this respect, to Professor R. Sievert,

Head of the Radiophysical Institute, for his generosity in placing at my disposal both technical staff and the technical resources of his institute. I also wish to thank Dr. B. Sylvén, Dr. S. Benner and Mr. A. Egmark for their very valuable contributions at the start of the laboratory work.

To Mrs. Inger Ragnhult, physicist at the laboratory, I am extremely indebted. Without her work and careful supervision of the physical measurements this investigation would not have been possible. I greatly appreciate, too, the services of Mr. L. Jonsson, engineer of the laboratory, whose construction and care of the measuring instruments were of very great help; I also have to thank him for help with the drawings. To Dr. Jerzy Einhorn I am also very indebted for valuable help with the clinical work.

For excellent technical assistance my acknowledgments are due especially to Mrs. Astrid Michon-Bordes and Mrs. Margit Wallqvist. I also wish to record my thanks to all other nurses and technical assistants who facilitated this investigation.

For revising my English I am greatly indebted to Mr. Stanley Vernon.

For financial support I have to acknowledge my indebtedness to the Swedish Cancer Society, *Cancerföreningen*, and the King Gustaf V Jubilee Foundation.

Stockholm April, 1955

Lars-Gunnar Larsson

Introduction

One of the aims of this investigation has been to analyse the results of treatment and the incidence of complications in a series of radioiodine treated hyperthyroid subjects. Between 500 and 600 cases have so far been treated at Radiumhemmet; 370 of these were treated between 1951 and 1953 and have a sufficient observation time for analysis of the results. The author does not consider the results in this series as representative of the best that may be obtained with this method. Like all other methods, radioiodine treatment requires personal experience; and since, this series is the first of its kind treated at the hospital it is doubtless marred by several mistakes due to insufficient experience. I have found it to be an important task to analyse the series in the hope of finding whether the principles of treatment employed require modification in order to ensure prompter control of the disease and less complications.

The investigation also had another practical clinical aim; namely, to study the behaviour of the radioiodine tracer tests after the treatment. No laboratory tests are simpler or more natural to perform, in connection with radioiodine treatment, than these tests; and it is of great clinical importance to know if they can also be used as diagnostic aids during the management of the patients after the treatment.

The literature on diagnostic and therapeutic measures in hyperthyroidism is very extensive. The references in this work have been confined to investigations performed with radioiodine; earlier papers on, for instance, the iodine metabolism or on other types of radiologic treatment of toxic goiters have been omitted.

Statistical analysis of the results of the investigations has been omitted, and would probably have afforded very little additional information in the present series. As far as possible the primary material has instead been illustrated graphically in such a way as to make the variations quite clear.



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CHAPTER I

Some Comments on the Tracer Tests with Radioactive Iodine

1. The Iodine Metabolism: A Brief Review

Since radioactive iodine was first used, in 1938, for physiologic studies (*Hertz, Roberts and Evans*, 139; *Hamilton* 124), that agent has assumed enormous importance in studies of the thyroid function in health and disease. An understanding of the tracer tests used for diagnostic purposes also requires some knowledge of the iodine metabolism, and in the following brief review will be summarized some of the principal facts.

The ingested iodine is rapidly absorbed in the gastro-intestinal tract. It is distributed in the blood and diffuses into the extracellular fluid of the tissue and into other body fluids. Besides the thyroid gland, some excretory glands, notably the salivary glands and the gastric mucosa, possess the ability to concentrate iodine and to secrete considerable amounts of inorganic iodide, most of which, however, is reabsorbed in the gastro-intestinal tract (*Myant et al.* 219; *Albert* 2). The bulk of the iodide in the body is either taken up by the thyroid and bound in organic form, or is excreted by the kidneys; only insignificant amounts are discharged in the saliva, sweat and feces.

The thyroid gland concentrates inorganic iodide from the blood, synthesizes and stores the thyroid hormone, and secretes the hormone to the blood stream. The inorganic iodide in the thyroid is freely exchangeable with the iodide in the blood, and the iodide concentrations in these two compartments thus maintain equilibrium with each other, the iodide in the thyroid, however, being much more concentrated (*Vanderlaan et al.* 352—355; *Wolff et al.* 378—380; *Astwood* 15, 16; *Wynngaarden et al.* 382—384). A portion of the iodide in the thyroid is continuously utilized for hormone synthesis. After being oxidized to iodine it combines with tyrosine in the thyroid proteins during the formation of mono- and di-iodotyrosine, from which the thyroid hormones, thyroxine and tri-iodothyronine, are formed. The bulk of these iodinated amino acids is stored in protein-bound form (thyroglobulin); only a minor part may be found in free form (*Taurog et al.* 340—342; *Gross et al.* 112, 113; *Roche et al.* 274—276). One important advance in thyroid physiology during recent years is the

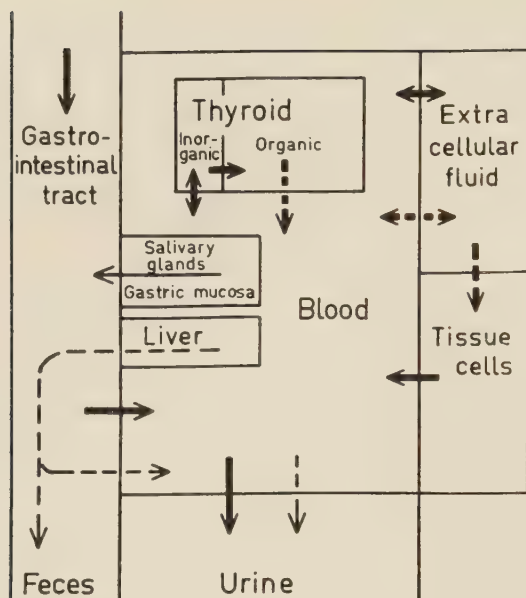


Fig. 1. Diagram of the iodine metabolism (mainly after *Riggs*, 268). Continuous arrows represent inorganic iodide and broken arrows represent organic iodine.

identification of tri-iodothyronine (*Gross et al.* 112—120; *Roche et al.* 274—276). This substance has been identified both in the thyroid and in blood plasma. Qualitatively it possesses pharmacologic characteristics similar to thyroxine, but is several times more active and has a faster action (*Gross and Pitt-Rivers* 117, 119; *Lerman* 183; *Asper et al.* 13). It is not definitely known if tri-iodothyronine in plasma is secreted from the thyroid or is formed peripherally from thyroxine; the first-mentioned alternative seems, however, very likely (*Gross and Pitt-Rivers* 120). Before the thyroid hormone passes into the blood stream, it is split off from the thyroid proteins, probably under the influence of a proteolytic enzyme (*De Robertis* 75). In the blood it is again bound to a protein, mostly to a globulin fraction (*Gross et al.* 115; *Albright et al.* 4, 74; *Gordon et al.* 107; *Horst* 154) but a part to the albumin (*Horst* 154; *Robbins et al.* 269).

From the blood the thyroid hormone diffuses into the extracellular tissue fluid and enters all the body cells, where it exerts its physiological action. During the metabolization, inorganic iodide is liberated, which enters the iodide compartment of the body and again follows the same pathways as the exogenous iodide (*Albert et al.* 3, 29, 163; *Myant et al.* 220). One part of the organic iodine in the blood is also excreted in the bile, some of it then being reabsorbed

in the intestine and some excreted with the feces (*Albert et al.* 3, 29, 163; *Myant et al.* 220; *Rall et al.* 256; *Roche et al.* 282; *Taurog et al.* 334, 335). A small part of the organic iodine in the blood is also excreted in organic form in the urine (*Rall*, 254).

The chief pathways for the iodine metabolism are schematically illustrated in Fig. 1 (mainly after *Riggs*, 268). When the iodide in the body is labelled with a tracer dose of radioactive iodide, either given by mouth and rapidly absorbed in the gastro-intestinal tract, or directly injected into the blood stream, it follows the same pathways as the stable iodide and gives a dynamic picture of the iodine metabolism. Alterations in the thyroid function will also change the way in which iodine is handled by the gland, which in several respects influences the behaviour of a given tracer dose of radioiodine. The tracer tests most used in practice are based upon measurements of the urinary excretion of radioiodine, measurements directly over the thyroid, and determinations of the concentration of inorganic or organic radioiodine in the blood. The tracer tests may be schematically divided into two groups: tests of the accumulation of I^{131} in the thyroid, and tests of the release of organic I^{131} (labelled hormone) from the thyroid. As the thyroid stores iodine, the accumulation of I^{131} in the gland will proceed at a much higher rate than the release of organic I^{131} from the gland, so that these phases may be analyzed more or less separately.

2. Tests Based on the Accumulation of I^{131} in the Thyroid

Estimation of the total uptake. — Provided that the release of organic I^{131} from the thyroid could be completely ignored, the percentage of a given tracer dose taken up by the thyroid gland would asymptotically approach a limit value (T_{∞}), and the total urinary excretion of the tracer dose another limit value ($U_{\infty} = 100 - T_{\infty}$). These values are of major interest, since they indicate what proportion of the ingested iodine is utilized for hormone synthesis. If an average steady state is assumed (*i.e.* the average amount of iodine organically bound in the thyroid per unit of time equals the average amount of secreted hormonal iodine per time unit), these values will have a simple quantitative relation to the hormone secretion (*Riggs* 268):

$$\frac{T_{\infty}}{100} = 1 - \frac{U_{\infty}}{100} = \frac{G}{G + I - F} \quad \dots\dots\dots (1)$$

where G is the daily secretion of hormonal iodine, I the daily intake of iodine, and F the daily loss of organic iodine from the body, mainly via the feces.

The value of T_{∞} cannot, of course, be directly determined. In practice, values which more or less approach T_{∞} are determined by repeated measurements over the thyroid with estimation of the maximal uptake or, more often, by a single measurement after a fairly long period, for instance 24 hours, when most of the radioiodine either has been excreted or has been taken up by the thyroid. Good values for T_{∞} may also be indirectly obtained by measuring the urinary excretion of I^{131} during the first few days after the administration.

Tests of the above-mentioned type were the first to be used (*Hamilton and Soley* 127, 128; *Hertz et al.* 134, 136, 142), and despite the elaboration of a large number of more refined tests they still possess considerable practical value due to their simplicity. The early literature on this subject has been reviewed in detail by *Skanse* (310) and *Kelsey et al.* (171) and will be omitted here. The most detailed study of a single test of this type — 24 and 48 hours urinary excretion — was made by *Skanse* (310), who studied the diagnostic value of this test in a large number of cases with thyroid disorders and in normal subjects. Both the 24 and the 48 hours urinary excretion enabled euthyroid and hyperthyroid patients to be well distinguished. As regards the distinguishing of euthyroid from hypothyroid subjects the 24 hours excretion was of very little value, but the hypothyroid subjects consistently showed a higher excretion from 24 to 48 hours than the euthyroid ones.

The directly measured uptake in the thyroid after 24 hours has also been extensively studied (*Werner et al.* 363—365, 368, 370, 251; *Freedberg et al.* 91—93; *Fields et al.* 86; *Greer* 110 and others). Due to anatomical variations as to size, shape and position of the thyroid, this method is associated with errors which vary from one patient to another and which are influenced by the geometry of the measuring technique and the method used for reduction of the secondary irradiation. The values given by different authors are also systematically influenced by the manner in which the compared standard solution of I^{131} has been measured. Despite these disadvantages, direct measurements over the thyroid are of great value and are necessary for many studies. As regards the 24 hours uptake in the thyroid, most authors have found that hyperthyroid subjects usually have values above 40—50 per cent and hypothyroid subjects values usually below 10—20 per cent. For reasons mentioned above, the values given by different authors are, however, difficult to compare.

In this investigation the thyroid uptake (T_{24}) and the urinary excretion (U_{24}) up to 24 hours were used as the routine tracer tests. Most of the patients in the series were treated while ambulatory, and for these patients the test was

rather convenient, whereas repeated measurements over the thyroid, or fractionated collection of the urine, would have entailed major practical difficulties. The combination of the two tests was expected to give more reliable information than either of the tests alone.

Technique. — Carrier-free I^{131} was obtained from Harwell. The tracer dose (30—100 microcuries) was given orally, and if only measurements after 24 hours were intended, no consideration was given to whether the patient was on an empty stomach or not. The urine was collected in 3-litre bottles, to which potassium hydroxide was added in order to ensure an alkaline reaction during collection. Careful instructions were given to the patients about the importance of quantitative collection of the urine. After dilution of the urine with water to a standard volume, it was measured in the same bottle by a gamma-method and compared with a standard solution of I^{131} measured under the same geometrical conditions. In the earlier part of the series a single gamma-sensitive G.M. tube was used, placed sufficiently far from the bottle to provide good geometry. In the greater part of the series a more convenient method was used, with six gamma-sensitive G.M. tubes (G 10 Pb, 20th Century) arranged in a circle round the bottle, thus providing good geometry despite the short distance (*Veall et al.* 359, *Freedberg et al.* 437).

Due to technical advances, the method used for direct measurements over the thyroid was not the same throughout the series. For reasons mentioned below, the values obtained with the different techniques were fairly well comparable and, therefore, have not been analyzed separately in the following. In a small proportion of the cases in the beginning of the series, an end-window G.M. tube was used. This instrument was later replaced by a gamma-sensitive G.M. tube (G 10 Pb, 20th Century), placed transversely in front of the thyroid. Lastly, a scintillation counter was used with a cylindrical thallium-activated sodium iodine crystal, 2.5 cm in diameter and with a thickness of 2 cm. The scintillation counter was provided with a single discriminator, so adjusted that all the gamma qualities from I^{131} were measured. All the instruments were fitted with wide-angle lead collimators and were adjusted to a distance of 27 cm from the anterior surface of the neck, with the patient recumbent. The distance was adjusted by means of a simple optical device previously described by *Jonsson* (166), who also designed the two last-mentioned instruments used. The crystal had a free position in the inner part of the conical lead shield, to ensure that no part of the crystal would be hidden by the lead shield from any part of the thyroid, a principle previously used by *Egmark* (80). Variations due to secondary radiation were, in all the instruments, reduced by a 2 mm thick lead filter. Like previous authors (*Fields et al.* 86), we found that with this filter the difference could be ignored when an I^{131} source was measured in air or water. This was true of both the G.M. tube and the scintillation counter. With the last-mentioned instrument a pulse spectrum was obtained by means of a channel pulse height analyser from an I^{131} source in air and water (*Ragnhult, Jonsson*), and the spectra almost coincided when the radiation was filtered with 2 mm lead. Similar findings have since been reported (*Hine et al.* 147). The standard solution of I^{131} was measured in a volume of 20 ml in a cylindrical vessel with a diameter of 3.5 cm, at a distance of 27 cm from the counter to the surface of the fluid. The counting rate measured over the neck was expressed in per cent of that measured over a standard solution containing the same activity of I^{131} as that given to the patient. Fig. 2 illustrates iso-sensitivity curves for the scintillation counter and the G.M. counter (G 10 Pb). They are so similar that no significant differ-

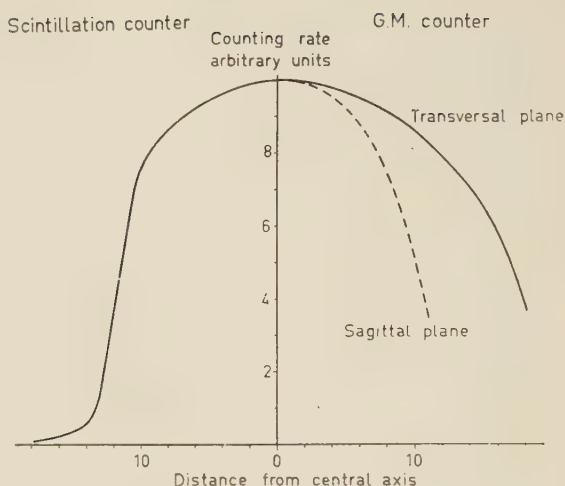


Fig. 2. Iso-sensitivity curves for the G.M. counter and the scintillation counter used for direct measurements of the thyroid uptake. Distance 27 cm.

ence can be expected due to varying extension of the thyroid. A series of circular Petri vessels were filled to a height of 2 cm with an I^{131} solution having the same total activity in all the vessels, and comparative measurements were done with the G.M. tubes and the scintillation counter, at a distance of 27 cm. As regards the scintillation counter and the transverse G.M. tube, the differences were within ± 1.5 per cent when the diameter of the vessel varied from 5 to 20 cm. The end window tube, used only in a minor part of the series, had of course a narrower iso-sensitivity curve; but with the distance used, the difference was also negligible here up to a vessel diameter of 10 cm — an extension only rarely exceeded by any goiters in this series. As regards counting statistics, we tried to keep the relative error in the end result (CPM source — CPM background) below ± 2 per cent. When the uptake or the urinary excretion was very low, this was not always possible, but in these cases a larger relative error may be tolerated.

An analysis of the diagnostic value of the tests is beyond the scope of this investigation. The material illustrated in Fig. 3 gives, however, despite its selected nature, a general idea of the type of information obtained and also of the correlation between T_{24} and U_{24} .

The hyperthyroid cases include the results of the tracer tests that preceded the first therapeutic dose in all cases treated in this series; patients who had received iodine treatment during the last year, or treatment with thiouracil derivatives during the last three months, were omitted. The euthyroid controls (102 cases) were taken from the wards and the out-patient department of Radiumhemmet and represented cases without any suspicion of thyroid disease. Many of the patients had, or had been cured of, malignant tumours, but only those in good general condition were selected; patients with known renal or heart disease were omitted. They were carefully questioned about the intake of iodine medicaments, roentgen examination of the gallbladder, etc, and were included only if no excessive iodine intake during the last year was known. The hypothyroid

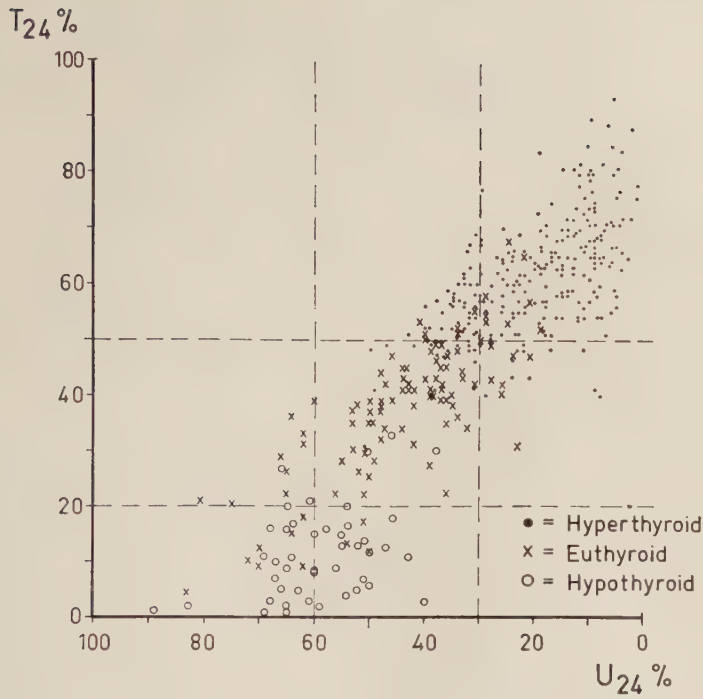


Fig. 3. Distribution of 24 hour thyroid uptake (T_{24}) and 24 hour urinary excretion (U_{24}) in 259 hyperthyroid subjects, 102 euthyroid controls and 44 hypothyroid subjects.

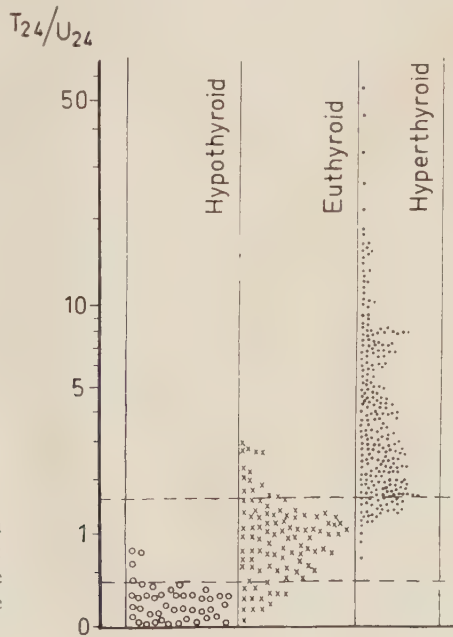


Fig. 4. Distribution of the quotient T_{24}/U_{24} in the same series as illustrated in Fig. 3. [Scale: $\log(n+1)$. This scale is usually used in the following when values of this quotient are presented.]

patients (44 cases) represented the cases with permanent post-radioiodine hypothyroidism in this series, and in each patient only the tracer test that immediately preceded the start of substitution therapy was included.

As will be seen from Fig. 3, there was considerable overlapping of the groups with respect to both T_{24} and U_{24} , but most pronounced in the case of U_{24} . If 20 and 50 per cent are taken as "normal" limits for T_{24} , then 13 per cent of the euthyroid controls had values above the upper limit and 10 per cent values below the lower limit; 13 per cent of the hyperthyroid cases had values equal to or below the upper limit, and 16 per cent of the hypothyroid cases values equal to or above the lower limit.

As regards U_{24} there was a high degree of overlapping. If 30 and 60 per cent are taken as "normal" limits, then 15 per cent of the controls had values above the upper limit and 15 per cent values below the lower limit. Of the hyperthyroid cases, however, 26 per cent had values equal to or above the lower limit, and of the hypothyroid ones 54 per cent had values equal to or below the upper limit. The average sum of T_{24} and U_{24} was, with the technique used, about 80 per cent, but, as shown in Fig. 3, it was considerably lower especially in the hypothyroid cases and in one group of the hyperthyroid ones. This was certainly due to the well-known fact that in hypothyroid cases an unusually large amount of radioiodine still circulates in inorganic form, and that in some hyperthyroid cases a considerable amount circulates in organic form, being already released from the thyroid as labelled hormone.

The average values for T_{24} and U_{24} were in the hyperthyroid series 61.6 and 20.0 per cent, and in the euthyroid controls 37.5 and 43.9 per cent, with a distribution illustrated in Fig. 5. In Fig. 6 the grouping is the same as that later used in presenting the results of treatment (primary diffuse toxic goiter, recurrent diffuse toxic goiter, primary hyperthyroidism without demonstrable goiter, and toxic nodular goiter). The series is, of course, not representative of unselected hyperthyroidism. Nevertheless, it is of interest to note that the average values were fairly uniform in the different groups, even in toxic nodular goiter, where considerably lower uptakes have sometimes been reported (*Seed et al.* 295, 296). The slightly lower uptake observed in some cases of nodular goiter may be due, at least in part, to the greater error caused by tissue absorption and the increased distance from the skin to the center of the radiation source in these, often larger, goiters.

The use of T_{24} and U_{24} combined is probably better than that of T_{24} alone, especially because of the rapid release of organic I^{131} from the thyroid in one

Fig. 5. Distribution of T_{24} and U_{24} in the total series and in the euthyroid controls. The sum of the columns in each group represents 100 per cent of the cases.

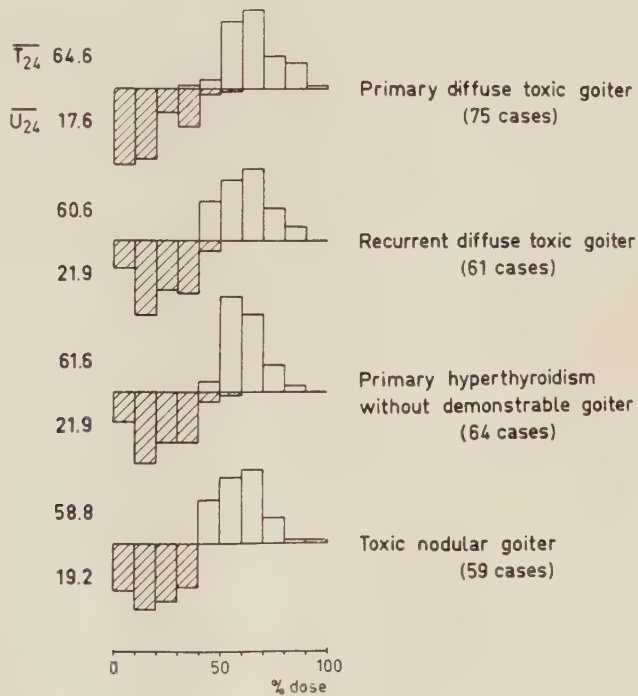
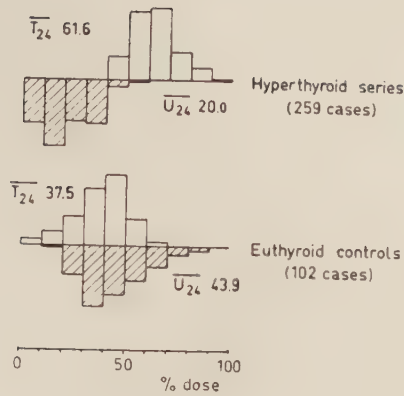


Fig. 6. Distribution of T_{24} and U_{24} in the different types of toxic goiters.

group of hyperthyroid patients. In this study, I have used the quotient of T_{24}/U_{24} as a rough expression of the radioiodine-concentrating capacity of the gland. In hypothyroid patients this expression usually gives low values even if U_{24} is indistinguishable from the normal range, and in hyperthyroid patients with a rapid release of I^{131} from the gland it gives usually high values even if

T_{24} lies in the normal range. The expression also has a definite theoretical basis. As will be seen from formula (1), the following expression may be obtained, still assuming an average steady state:

$$\frac{T_{\infty}}{U_{\infty}} = \frac{G}{I - F} \dots\dots\dots (2)$$

Provided that the measurement is done when all the I^{131} in the thyroid may be regarded as organic, and provided that the release of labelled hormone may be ignored, this expression will be equal to T/U at any time. The expression has a simpler quantitative relation to the hormone secretion than in any other tracer test. In practice the value of this quantitative relation should not, of course, be overestimated; if T_{24}/U_{24} is used, the release of organic I^{131} from the thyroid may seriously influence the values, and inadequate collection of the urine will also result in large errors. Nevertheless, the expression was found useful in this series, especially as a means of following the changes in the tests after treatment, and it is used for presentation of some data in Chapters II and III. Fig. 4 shows the values for T_{24}/U_{24} in the same series as that in Fig. 3. If 0.4 and 1.6 are taken as "normal" limits, 13 per cent of the controls had values above the upper limit and 12 per cent values below the lower limit. Nine per cent of the hypothyroid cases had values equal to or above the lower limit, and 13 per cent of the hyperthyroid cases values equal to or below the upper limit.

Tests Based on Early Measurement of the Thyroid Uptake. — Measurement of the thyroid uptake at an earlier stage after the administration usually enables a better distinction to be made between the different functional states. There are two reasons for this. The first is that the differences between the average plasma concentrations of I^{131} in different individuals are less pronounced from, for instance, 0 to 2 hours than they are from 0 to 24 hours. The other lies in the rapid secretion of labelled hormone that occurs in some hyperthyroid patients. Several authors have therefore preferred uptake measurements after, for instance, 1—6 hours (*Miller et al.* 208; *Kriss* 175; *Greer* 110; *Horst* 151, 152 a.o.). As regards the very early uptake measurements, intravenous injection of the tracer dose is preferable in order to avoid variations due to absorption in the gastrointestinal tract. However, after oral administration the uptake may already be used after one hour, provided that the tracer dose is given on an empty stomach (*Crispell et al.* 71).

In one part of this series the 3 hours uptake was used. The measurements were as described in the 24 hours uptake, and the results are reported in Chapter III. No correction was made for body background, and only measurements done with the scintillation counter are included. The tracer dose was given orally on an empty stomach.

As pointed out in a previous report (*Larsson and Jonsson 1979*), even the thyroid curve for the first few minutes may be used for diagnostic purposes, provided that the counting rates over the neck are continuously recorded after an intravenous tracer dose.

Technique. — The scintillation counter was adjusted in the same way as described earlier. The counting rates were registered by a counting rate meter combined with a direct-writing instrument (Speedomax). Usually a time constant of 2.5 seconds was used for the rate meter. The tracer dose was injected rapidly into a brachial vein and 30 microcuries was sufficient for obtaining evaluable curves.

Immediately after the injection a high peak was obtained, due to I^{131} passing the great vessels (Figs. 7 and 9). After about 30—60 seconds a more or less ascending curve was usually obtained in hyperthyroid and euthyroid subjects and, due to the diminishing body background and the low thyroid uptake, a more or less descending curve in hypothyroid subjects (Figs. 7 and 9). The measured counting rates were, as in the 24 hours uptake, expressed in per cent of the counting rate from the standard solution, and for the sake of convenience the values are called “the neck uptake” (H). For practical diagnostic purposes the curves were most easily analyzed by taking the difference between the H values at two points in time. The type of discrimination obtained is illustrated in Fig. 41, Chapter III, where the change in H during a 10-minute interval from 1 to 11 minutes was used ($H_{11} - H_1$).

If, for physiologic purposes, a more exact thyroid curve during the initial phase after the injection is required, the method makes possible a more accurate correction for body background (*i.e.* radiation from I^{131} outside the specific thyroid tissue) than has hitherto been the case. Two main methods have previously been described for correction for body background. The first is based on parallel measurements over the neck and over the thigh, and subtraction of the thigh values from the neck values (or usually the thigh values multiplied by a correction factor, as the amount of I^{131} in a section of the thigh differs from that in the extrathyroid tissues of the neck). Since the blood/tissue ratios in the neck and in the thigh are very different (higher in the neck), this type of background correction cannot be used until the concentrations of radio-

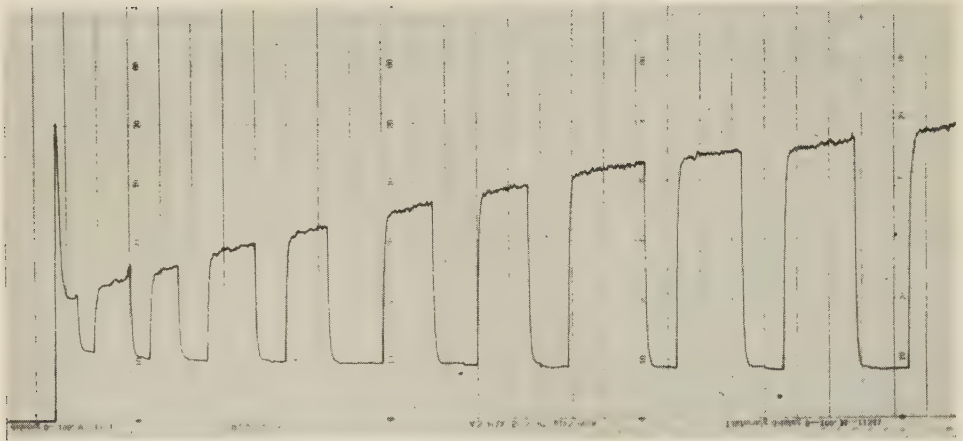


Fig. 7. Result of continuous measurement over the neck in a hyperthyroid patient after intravenous injection of I^{131} in a brachial vein. The lower curve represents the values obtained when the thyroid gland was covered by a thick lead shield, leaving a zone of neck tissue still "seen" by the scintillation crystal. The interval between two vertical lines is one minute. [For purposes of demonstration the measurements were done after a therapeutic dose (4 mC). After a small tracer dose the curves are more oscillating due to statistical variations, but the equalizing curves are scarcely more difficult to draw, provided that the counting rates have been continuously recorded.]



Fig. 8. Same case as in Fig. 7. The principle of the body background correction described in the text is illustrated.

iodine in the blood and in the tissues have approached equilibrium, as has also been pointed out by several authors (*Childs et al.* 60; *Greer* 110; *Myant et al.* 219, 220; *Blom* 34). The discrepancy between the thigh curve and the neck background curve is clearly demonstrated in Fig. 10, showing a patient with complete myxedema who, for good reasons, could be regarded as "athyrotic". She had previously undergone hemithyroidectomy for a malignant thyroid adenoma. Due to a peripheral metastasis the remaining small thyroid lobe, which took up 33 per cent of a tracer dose, had been destroyed with 100 mC I^{131} . Since then repeated tracer tests with detailed measurements by directional scintillation counter had failed to reveal any localized uptake of I^{131} in the neck. The neck curve showed the type usually seen in myxedema, with a continuously descending curve due to the diminishing neck background. There was a major discrepancy between the neck curve and the thigh curve, and the curves had also very different shapes, so that even the use of a correction factor for the thigh curve would have been insufficient.

Another method for neck background correction was introduced by *Berson et al.* (32). They measured the counting rate over the neck during the first few minutes after the intravenous injection, and regarded this value as representative of the neck background at zero time; and they then measured the urinary excretion and the uptake after a certain time. By assuming that the extrathyroid radioiodine had the same distribution in the body throughout the period, the neck background could be theoretically calculated. — The present writer used this method during one period and found that it usually gave an over-correction, so that negative values were obtained in cases with very low uptake; the same was recently observed by other investigators (*Hanbury et al.* 132). It is obvious for two reasons that an over-correction must be obtained. Due to the higher blood/tissue ratio in the neck than in other parts of the body, the neck background shortly after an injection has quite a different relation to the total body content of I^{131} than that after a period when much of the radioiodide has diffused into the extracellular fluid. The other reason is that in patients with a rapid uptake of I^{131} in the thyroid, this may already be considerable after the first few minutes.

In this investigation another type of body background correction was used. After the injection of I^{131} the continuous measurements over the neck were done both alternately as previously described and alternately with the thyroid covered by a thick lead shield (3.5 cm, absorbing about 99 per cent of the I^{131} irradiation) with a diameter of 10 cm, covering the whole thyroid but leaving

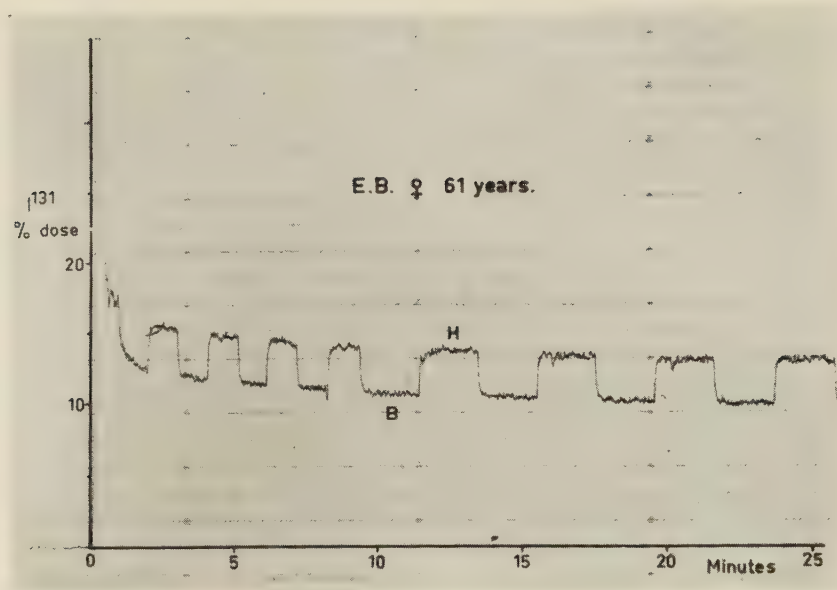


Fig. 9. Continuous measurement over the neck after intravenous injection of I^{131} in a patient with complete myxedema. The upper curve represents the measurements when the thyroid region was uncovered (H) and the lower curve when it was covered with a thick lead shield (B), leaving a zone of uncovered neck tissue still "seen" by the crystal. The slope of the two curves is very similar, indicating that very little or no radioiodine was taken up by the gland.

a zone of uncovered neck tissue still included by the wide-angle collimator and "seen" by the crystal. The lead shield was fixed in a constant position to the counter about 1 cm above the neck, and in all cases in which this method was used the thyroid had been outlined with a directional scintillation counter after an earlier tracer dose, in order to ensure complete covering. In this way two curves were obtained (Figs. 7 and 9), one when the thyroid was uncovered (H) and one when it was covered (B). After the injection the counts taken over the neck derive from three sources: I^{131} in the blood, I^{131} in the extracellular fluid, and I^{131} taken up by the specific thyroid tissue. The first two sources represent the neck background. Both curves H and B were extrapolated back to zero time, ignoring the first minute, which included the mixing phase in the blood and the initial peak. H_0 and B_0 were regarded as the theoretical neck background at zero time, in the total field and in the uncovered zone respectively, assuming that the injected I^{131} could have been instantaneously mixed in the blood stream. H_0 was independent of the iodide-

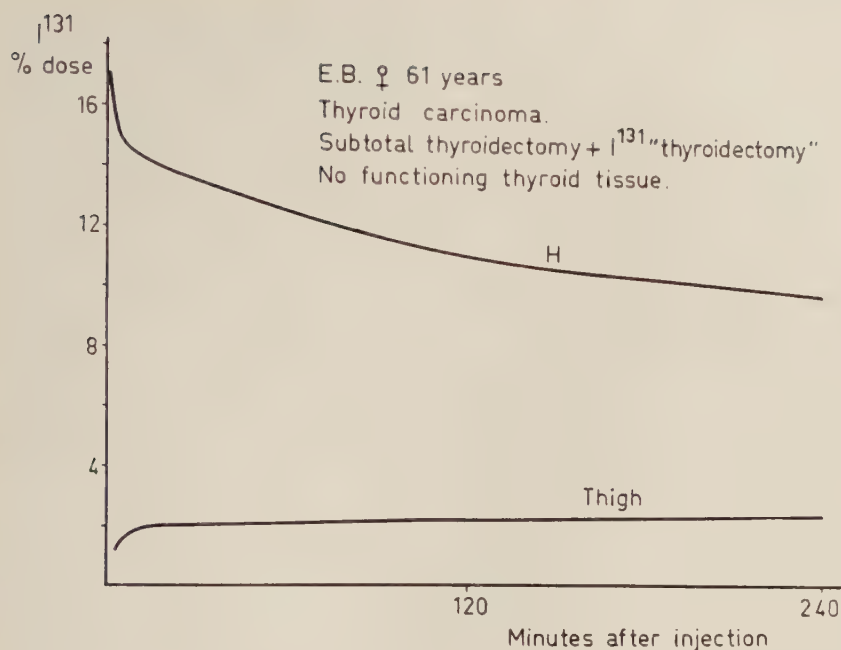


Fig. 10. Same patient as in Fig. 9. The measurements were performed alternately over the neck (H) and over the thigh after intravenous injection of I^{131} . The same distance (27 cm) and the same shielding was used for both measurements. Previous detailed measurements by directional scintillation counter had failed to reveal any localized uptake in the neck, and curve H represents, in all probability, only background radiation from circulating I^{131} . Note the different shapes of the neck and thigh curves.

concentrating capacity of the gland and, in hyperthyroid and euthyroid subjects, had the same value before and after administration of 2 gm sodium thiocyanate, which considerably inhibited the iodide-concentrating function of the thyroid. On the assumption that the blood/tissue ratio was the same in the part covered by the shield as in the uncovered part, curve B was multiplied by the correction factor H_0/B_0 , and the curve obtained was subtracted from H in order to get the thyroid uptake curve (T). Figs. 7 and 8 show an example of this type of background correction in a hyperthyroid patient. In Fig. 9 the method has been used in the aforementioned "athyrotic" patient and shows that curves H and B have a very similar slope, indicating that very little or no radioiodine was taken up by the thyroid. One error may lie in the assumption that the blood/tissue ratio is the same in the covered as in the uncovered part of the neck, but the difference in this respect is certainly less than that between the neck and, for instance, the thigh (Figs. 9 and 10). Another error lies in the

extrapolation of the two curves back to zero time. The error in this extrapolation is, in most cases, probably rather small, as demonstrated in cases where H_0 was determined before and after thiocyanate administration. Some cases of hyperthyroidism have an extremely rapid initial uptake, and a considerable amount may also have been taken up during the first minute. The steep initial course of the curve may, in such cases, make the extrapolation difficult. However, such cases were seldom seen in this series, and even in these cases it should be possible to determine point H_0 with satisfactory accuracy if a tracer test is later repeated after thiocyanate administration with a new determination of H_0 . As mentioned above, this somewhat complicated method for body background correction is unnecessary if the test is done only for practical diagnostic purposes. Since it was used in this study for a special investigation reported in Chapter III, it has been described in detail.

One objection may be raised against all of these early uptake measurements as diagnostic tests. The ability of the thyroid to concentrate the iodide ion from the plasma is, in part, independent of its hormone-synthesizing function (*Van derlaan et al.* 352—355; *Wolff et al.* 378—380; *Chaikoff et al.* 51 and others). If the capacity of the gland to bind the iodine organically is depressed, but its iodide-concentrating ability preserved, a considerable amount of a tracer dose of I^{131} may be found in the gland during an early stage when the plasma concentration of radioiodide is still high. In such cases the early uptake measurements give a false impression of the thyroid function; *i.e.*, its capacity to utilize iodine for hormone synthesis. The best known example of this mechanism is treatment with drugs of thiouracil type (*cf. Astwood* 15). Impaired organic binding of iodine, with retained iodide-concentrating capacity, has also been reported in some goitrous cretins, while in others the disturbance of the iodine metabolism in the thyroid seems to be even more complicated (*Stanbury et al.* 322, 323). It does not seem unlikely that minor discrepancies between the iodide-concentrating function and the ability to bind the iodine organically may occur, too, in other types of atoxic goiters; and a more comprehensive study of the “initial neck curves” will therefore be required before the possibility of using this test for routine diagnostic purposes can be determined. In cases of hyperthyroidism both the rate at which the radioiodide diffuses into the thyroid and the rate of organic binding are certainly increased. It seems natural, therefore, that the “initial neck curve” in most cases of hyperthyroidism will show values quite distinct from those in euthyroid subjects, which also is demonstrated in Fig. 41.

Estimation of Characteristic Rate Constants. — Other factors than the capacity of the thyroid to accumulate radioiodine influence the behaviour of a given tracer dose; they include notably the renal function. It should, therefore, be more accurate to determine the rate at which I^{131} disappears from the plasma to the thyroid, than to measure the uptake or urinary excretion up to a fixed time. *Keating et al.* (167—169, 171) introduced the accumulation rate or extra-renal disposal rate, *i.e.*, the fraction of the body radioiodide which is bound to the thyroid per unit of time when the radioiodide has approached equilibrium within the total iodide compartment of the body (plasma + body tissue + thyroid). They found that the plasma curve had a simple exponential slope after about one hour, indicating that radioiodide after that time had approached equilibrium within the total iodide compartment and was then mainly released therefrom by being fixed in organic form in the thyroid and excreted by the kidneys. Just as the plasma concentration curve had a simple exponential course, so was the rate of urine excretion after that time simply exponential, and by fractional collection of the urine the two rate constants for the disappearance of I^{131} from the iodide compartment to the thyroid and to the urine could be calculated. The accumulation rate could also be directly estimated from the thyroid uptake curves. Other tests based on a similar principle have been devised (*Nitkowsky et al.* 224, *Oddie* 225, *Brownell* 42, *Rotblat et al.* 285).

A somewhat similar type of analysis is the thyroid clearance introduced by *Myant et al.* (222) and *Keating et al.* (168). If it is assumed that all the radioiodide taken up by the gland will be organically bound and also that the release of organic I^{131} from the gland can be ignored (which may be done in all euthyroid patients for several hours, and in most hyperthyroid patients for at least the first hour or two), the following expression will be obtained:

$$\frac{dT}{dt} = C_T \cdot P \quad \dots\dots\dots (3)$$

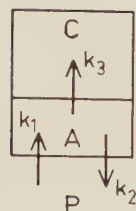
If P is the concentration of I^{131} in the plasma, expressed in per cent of dose per liter, and t the time in hours, the thyroid clearance C_T will be expressed in liters per hour. Since this formula involves the drawing of a tangent to the thyroid curve, the integrated formula is more suitable for practical work:

$$C_T = \frac{T_2 - T_1}{\int_{t_1}^{t_2} P \, dt} \quad \dots\dots\dots (4)$$

i.e., the difference between the uptakes at two points in time is measured and divided by the average plasma concentrations of I^{131} during this period and the length of the period. Both the extrarenal disposal rate and the thyroid clearance have been extensively studied and have been found to afford a fairly clear distinction for diagnostic purposes, but with these tests, too, there is an appreciable degree of overlapping of different functional states (*Keating et al.* 168; *Myant et al.* 222; *Goodwin et al.* 105). Characteristic of both types of tests is that the values are numerically distributed over a very wide range. While normal subjects usually have C_T values between 10 and 60 ml per minute, hyperthyroid subjects often have values of several hundred milliliters per minute, and even values above one liter per minute may be noted.

One of the main reasons for the introduction of these methods was that the uptake of I^{131} in the gland is also influenced by extrathyroid factors, especially the renal clearance of iodide. It is obvious that renal failure should increase the plasma concentrations of I^{131} , and hence change the amount of I^{131} available for the gland to take up. The mechanism in this respect is, however, not so simple as was first assumed. When radioiodide is retained in the body due to renal failure, there is also a retention of stable iodide in the body, with increased iodide concentrations, assuming the average iodide intake to be constant. This has, in fact, the same influence as an increased iodine intake, *i.e.*, the accumulation rate of I^{131} decreases (*cf. Riggs* 268; *Perry et al.* 240). If the tracer tests are analyzed from a quantitative point of view (*Riggs* 268) it will be found that a simple expression as T_∞ is independent of the renal function, in contrast to more complicated tests such as the accumulation rate and the thyroid clearance. In cases with renal failure, however, the urinary excretion and the uptake of I^{131} in the thyroid proceed slowly, with cumulative curves gradually ascending over a long period, due to the decreased accumulation rate and excretion rate and to the fact that the blood concentrations are relatively high for a long period (*Skanse* 310; *Perry et al.* 240). The methods which determine the thyroid uptake and urinary excretion up to a fixed time, for instance 24 or 48 hours, will therefore give values which fall, to a greater extent than usual, below T_∞ and U_∞ , thus providing erroneous information about the thyroid function. From practical point of view it can be said that the combination of renal failure and hyperthyroidism is relatively uncommon (*cf. Skanse* 310). In this series of radioiodine treated hyperthyroid patients it did not constitute a practical problem, and it seems unlikely that renal failure influenced the values other than in exceptional cases.

Fig. 11. Diagram of the interrelation between plasma and thyroid radioiodine. P is the concentration of inorganic radioiodide in plasma, A the amount of inorganic radioiodide, and C the amount of organic radioiodine in the thyroid; k_1 , k_2 and k_3 are rate constants for the different transfers.



Since the iodide ions in the thyroid are freely exchangeable with the iodide ions in the plasma, the interrelation between plasma radioiodide and radioiodine in the thyroid is more complicated than expressed in formulas 3 and 4. The course of events may be schematically exemplified as in Fig. 11, where P is the plasma concentration of radioiodide (per cent of dose per liter), A the inorganic iodide in the thyroid (per cent of dose), C the organic iodine in the thyroid (per cent of dose); k_1 is the rate of transfer of radioiodide from plasma to thyroid (liters per hour), and k_2 and k_3 rate constants for, respectively, the transfer of inorganic iodide from thyroid to plasma and for the organic binding of iodine in the thyroid (proportion per hour). The diagram is, of course, a simplification as the release of organic I^{131} from the thyroid to the blood has been omitted, and also the release of inorganic radioiodide from the iodinated amino acids in the thyroid to its iodide compartment (*Roche et al.* 281). However, both of these transfers probably proceed rather slowly, so that they can be omitted for the initial period after the injection as long as the plasma concentration of radioiodide is still high. The interrelation between plasma and thyroid radioiodine can thus be described by the following expressions:

$$T = A + C \quad \dots\dots\dots (5)$$

$$\frac{dA}{dt} = k_1P - k_2A - k_3A \quad \dots\dots\dots (6)$$

$$\frac{dC}{dt} = k_3A \quad \dots\dots\dots (7)$$

After the injection the quotient A/C asymptotically approaches a limit value, equal to the thyroid iodide space (*i.e.*, the volume required for the thyroid iodide to reach the same concentration as the plasma iodide). The expression k_1/k_2 is also of interest and represents the "theoretical" thyroid iodide space, *i.e.*, that which should be obtained if there were no organic binding at all in the

thyroid. To be correct, the thyroid clearance should not be calculated until equilibrium has been reached between radioiodide in the plasma and in the thyroid. Even then it would have a significant bearing only if the far greater part of the thyroid radioiodine were organically bound, so that T would be practically equal to C . It can thus be assumed that the thyroid clearance is not a constant expression (*Castenfors, Ek, Porjé*, 50), and since the initial phase after the injection is characterized by the rapid diffusion of radioiodide from the plasma into the thyroid, it should show diminishing values during the initial period. Nevertheless it has been found that the values for thyroid clearance at different times after the injection are often, but not always, fairly constant, provided that the determinations are made at a stage when the release of organic I^{131} from the thyroid may still be ignored (*Myant et al.* 222). With use of the previously described technique for measurement of the uptake and background correction, the author made similar observations in a series reported in Chapter III. This constancy may have two explanations. First, the rate of organic binding may be very high, so that k_3 will be considerably greater than k_2 (cf. *Rollinson et al.* 284). Secondly, radioiodide in the thyroid and plasma may quickly approach equilibrium, and by far the greater part of the radioiodine in the thyroid may then already be organically bound. The author has observed one thiouracil treated hyperthyroid patient in whom the thyroid curve (Fig. 55, curve 6, Chapter III) indicated almost completely abolished organic binding and the T/P ratio had reached, after only 15 minutes, a constant value. The time taken for this mixing, however, probably differs widely in different individuals, depending upon, for instance, the blood flow through the thyroid. That the bulk of radioiodine in the thyroid is very quickly found in organic form is best known from animal experiments; *Chaikoff et al.* (51) found that after only 15 minutes 95 per cent of I^{131} in the rat thyroid was organically bound.

If the organic binding of iodine is impaired, as in thiouracil treated subjects, the thyroid clearance will definitely lack significance. In these cases the thyroid uptake curve will be strongly influenced by the relatively large proportion of inorganic radioiodide in the thyroid. The quotient between the rate of uptake and the plasma concentration of I^{131} will in such case show rapidly decreasing values and may even fall to negative values at an early stage, due to the rapidly decreasing plasma concentrations of I^{131} .

Another empirical method for demonstration of impaired organic binding has been described by *Astwood and Stanley* (18, 327, 328). They found that

if the thyroid curves during the first few hours were plotted against the square root of time, they represented a straight line; the slope of this line was called the accumulation gradient. If the organic binding was impaired by agents of thiouracil type the curves had a differing appearance with a curved shape, due to the diminished ability of the thyroid to accumulate radioiodine in organic form. Both these methods are purely empirical and provide no numerical expression of the degree of organic binding.

A third method is based upon the observation that certain anions rapidly release the inorganic iodide from the thyroid. Of these, thiocyanate and perchlorate are the most active ones (*Vanderlaan et al.* 352, 355; *Stanley et al.* 328; *Wyngaarden et al.* 382, 384). The thyroid iodide space is increased in hyperthyroid subjects. If the organic binding is impaired, for instance by thiouracil treatment, the blood concentrations of I^{131} will still be so high after several hours that a considerable amount of I^{131} in the thyroid will be inorganic and releasable by thiocyanate. Similar release may also be obtained with iodide in excess, due to isotopic dilution of the diffusible radioiodide. Iodide, however, also has a more specific effect, and at sufficiently high plasma concentrations it inhibits the organic binding of iodine, with a retained thyroid/plasma gradient for the concentration of iodide (*Chaikoff et al.* 51; *Wolff et al.* 379; *Childs et al.* 60; *Stanley et al.* 326, 329).

The ideal method for full elucidation of the accumulation phase of I^{131} would be a numerical calculation of the different rate constants which determine the collection of I^{131} in the thyroid. Due to the complicated mathematical expressions that are obtained, *Rollinson et al.* (284) recently used an electrical analogy apparatus for numerical calculation of the constants from the empirical curves. They postulated five compartments for the radioiodine during the initial period after an intravenous injection, *i.e.*, blood, extrathyroid tissue, iodide compartment in the thyroid, organically bound iodine in the thyroid, and iodide in the urine; they also assumed that two of the transfers were "one-way streets", *i.e.*, blood $\rightarrow$ urine and inorganic $\rightarrow$ organic radioiodine in the thyroid. With the use of this model they analysed fractionated urinary excretion curves and were able, in this way, to assign numerical expressions to the different turnover rates. Only one case was reported — an untreated hyperthyroid patient. Of interest was the finding that k_3 in this case was about six times greater than k_2 , which implied that about 85 per cent of the radioiodide present in the thyroid at any given moment would become organically bound. If correct, this finding may explain why the thyroid clearance values in some cases are already

constant at an early stage after the injection. The method employed seems, however, very indirect, and with the complicated model used it is probably associated with rather large errors.

As will be seen from equations (5) to (7), the three constants k_1 , k_2 and k_3 are definitely determined by the thyroid uptake curve and the plasma concentration curve. For the calculation of all three constants, the first part of the curves must be used too, *i.e.*, before equilibrium has been reached between plasma and thyroid radioiodide. Such a calculation would be of considerable interest, but it is questionable if the thyroid curve can be determined with sufficient accuracy during this early period. As regards k_3 , which expresses the rate at which the iodide in the thyroid is organically bound, this constant may be calculated also from the later part of the curves when equilibrium has been reached. This method has been used by *Ingbar* (161, 162). He assumes that the mixing of radioiodide in the total iodide compartment is complete after about one hour, and, like other investigators, finds that the plasma concentration curve after that time has a simple exponential course. By extrapolating this part of the curve back to zero time on a logarithmic scale, he obtains the initial plasma concentration (P_0) that should be found if there were instantaneous complete mixing in the total iodide compartment after the injection. By selecting two points in time after one hour (t_1 and t_2) with the corresponding experimentally determined values of P_1 and P_2 and T_1 and T_2 , it is possible to calculate k_3 and the thyroid iodide space (S liters), and also to determine the theoretical value T_∞ . The following expressions were derived:

$$T_\infty = \frac{P_1 T_2 - P_2 T_1}{P_1 - P_2} \dots\dots\dots (8)$$

$$S = \frac{P_1 T_\infty - P_0 T_\infty + P_0 T_1}{P_1 P_0} \dots\dots\dots (9)$$

$$k_3 = k \cdot \frac{T_\infty}{S \cdot P_0} \dots\dots\dots (10)$$

(k being the rate constant for the disappearance of radioiodide from plasma expressed in fraction/hour).

The formulas will be valid if the assumed equilibrium for radioiodide in the iodide space is correct and if the release of organic I^{131} from the thyroid may be ignored. The first assumption is doubtless very much of an approximation. *Myant et al.* (219) demonstrated that the radioiodide space rapidly increased

during the first hour after an intravenous injection and then continued to increase more slowly for several hours, indicating that equilibrium was only gradually reached. However, provided that the plasma curve after one hour may be replaced, with sufficiently good approximation, by a simple exponential function, the only factor of importance in the calculation above will be that the thyroid and plasma radioiodide has approached equilibrium; and this probably occurs earlier than in the case of the total body iodide space. Ignoring of the secretion of labelled hormone will not, in most cases, cause any serious error.

It seems not unlikely that radioiodine treatment may damage the partial functions of the thyroid in varying degree. *Kirkland* (173) examined patients treated with I^{131} for hyperthyroidism and observed that many of them showed impaired organic binding of I^{131} in the thyroid, with retained capacity to concentrate the iodide ion. He based this finding partly on the type of thyroid uptake curves and partly on the release of I^{131} from the thyroid after thiocyanate administration. So far, *Kirkland's* report is the only one of its kind. As regards the analysis of the uptake curves, several objections may be raised to the technique used. A more detailed technique in this respect, especially with simultaneous registration of thyroid uptake curves and plasma concentration curves, might be expected to yield more reliable information and has been used in this investigation. The results are reported in Chapter III.

Technique. — After rapid intravenous injection of radioiodine the thyroid curves were continuously recorded and corrected for body background in the same way as before. The registration was continuous for at least the first 30 minutes, after which repeated measurements were done at intervals of 15—20 minutes. Blood samples were withdrawn (10 ml each) via a retained artery needle. Usually 8 samples were taken, from 5 to 120 minutes after injection, for the purpose of plotting a complete concentration curve for that period. After about 125 minutes, 2 gm sodium thiocyanate was given on an empty stomach, and the "neck curves" and "background curves" were recorded for a further 2 hours: the first half hour after the intake of NaSCN, continuously; then with repeated measurements every 15—20 minutes. The plasma I^{131} was measured in a liquid counter of Veall's type and compared with a standard solution of I^{131} . Thirty microcuries of I^{131} was sufficient as a tracer dose, but due to the nature of the cases larger tracer doses (0.1—0.3 mC) were usually justified and increased the accuracy. In some cases the investigation was made in connection with a small therapeutic dose (1—4 mC). The curves derived in this way were analyzed by several methods in order to find out whether there was any impaired organic binding. The quotient of the rate of uptake and the average plasma concentration was calculated in respect of successive 10 minute intervals from 5 to 115 minutes. If the organic binding were impaired, rapidly decreasing values might be expected, as in thiouracil treated subjects. The thyroid curves were also plotted against the square root of time, and bent curves of thiouracil type were expected if the organic binding was impaired. Lastly, the curves were analyzed by the aforementioned method of

Ingbar (161), with determination of the thyroid iodide space and the value of k_s . If there was impaired organic binding, a discrepancy between these two values could be expected. For t_1 and t_2 , 1 and 2 hours were regularly chosen. A detail of major importance to the result was not analyzed by *Ingbar*, namely, the influence of the neck background. When the uptake is large, this factor has no great importance, but in cases with a moderate or low uptake it has a considerable influence. As shown in Fig. 7, there will be a tendency to overestimate H_0 and underestimate B_0 , and the curve $\frac{H_0}{B_0} \cdot B$ can usually be regarded as an upper limit for the true background correction. Since the lead shield also removes part of the neck background, curve B represents a lower limit for this correction. The values reported in Chapter III were calculated both with $\frac{H_0}{B_0} \cdot B$ and with B as background correction, in order to elucidate the maximal unreliability of the values attributable to the neck background. *Ingbar* used, for correction, simple subtraction of the thigh values from the neck values. Except in cases with large uptakes, this procedure is bound to involve a considerable error, as the thigh value is only a fraction of the neck background when the same geometry is used for the measurements. The magnitude of the error depends upon the type of collimator used. This was not described in detail; *Ingbar* only mentioned that no radiation from the superior mediastinal structures was included and that the thigh measurements were performed with the same geometry as the neck measurements. At all events the thyroid curves must have been under-corrected — and this will generally result in too high values for the thyroid iodide space and too low values for k_s . It can be demonstrated that only minor changes in the factor by which the background curve is multiplied may cause fairly substantial differences in the calculated values for S and k_s , which must thus be regarded as somewhat rough approximations.

Tests of the Release of Organic I^{131} from the Thyroid

As soon as some radioiodine is bound to the thyroid in organic form, a release of I^{131} labelled hormone from the gland will start. This is a rather slow process, and as long as the plasma concentration of radioiodide remains high it will have no great influence on the thyroid uptake curve compared with the rapid accumulation of I^{131} in the gland. As the plasma concentration of radioiodide progressively decreases due to organic binding of I^{131} in the thyroid and elimination by the kidneys, the accumulation of I^{131} in the thyroid will proceed more and more slowly until a point is ultimately reached where the release of organic I^{131} from the gland exceeds the accumulation. The curve has at that point a maximum (glandular peak uptake). The disappearance of I^{131} from the gland will then, after a sufficient time, have a simple exponential course. In some hyperthyroid subjects the disappearance rate of I^{131} from the gland is initially more rapid than later, and not until a few days have elapsed will the curve show a simple exponential slope. The explanation normally given for this type of curve is the rapid metabolism of the labelled hormone, with

liberation of inorganic radioiodide reutilized in the thyroid. Another possibility is, however, that the thyroid secretes two labelled compounds (or the same compound from two different compartments in the thyroid) with different turnover rates (*Stanbury and Brownell*, 319). An expression for the rate of release of labelled hormone from the thyroid is the biological half-life (BHL) of I^{131} in the gland, which usually is much shorter in cases with hyperthyroidism than in normal subjects.

Simultaneously with the release of I^{131} from the thyroid there will be an increase in the organic fraction of I^{131} in the plasma. This increase has usually been studied by estimation of the protein-bound I^{131} fraction (PBI^{131}) after the use of common protein precipitating agents (*Chaikoff et al.* 52; *McConahey et al.* 191; *MacGregor et al.* 197, and others), or by estimation of the thyroxine-like fraction of I^{131} after butanol-extraction (BEI^{131}) and re-extraction with sodium carbonate (*Chaikoff et al.* 51; *Schultz et al.* 291, 292; *Ingbar et al.* 163). Both PBI^{131} and BEI^{131} are, after a sufficient time, increased in hyperthyroid patients, and have been found to be rather sensitive to diagnostic tests if determined after 1—3 days. The quotient of PBI^{131} and total I^{131} in plasma (conversion ratio) has also been used for diagnostic purposes (*Clark et al.* 61, 62, 302). When these tests were introduced, it was thought that they would provide a more direct expression of the hormone secretion than studies of the accumulation of I^{131} in the gland, and it was even suggested that they might be a convenient substitute for the more complicated estimation of stable protein-bound iodine in the blood (SPI). In this respect the tests have been disappointing and the original assumptions have proved to be wrong. Indeed, the methods which measure the accumulation of I^{131} in the gland have a much more simple and direct quantitative relation to the hormone production than those which measure the release of organic I^{131} from the thyroid (*Riggs* 268). The last-mentioned tests are also dependent, of course, upon the uptake of I^{131} in the gland. Provided that the uptake has the same order of magnitude it may be said, however, that these tests reflect the turnover rate at which organic iodine is secreted from the thyroid. But the total rate at which this secretion occurs is dependent, too, upon the storage of organic iodine in the thyroid. If this storage is low, even a high turnover rate may imply a normal or subnormal secretion and vice versa (*Tubiana* 350; *Blom et al.* 34, 35). After surgical and radiological treatment it must be assumed that the remaining mass of functioning thyroid tissue is extremely varying, and hence also the total iodine storage in the gland. It has also been found that tests as BHL and PBI^{131} may

show very "pathological" values in patients with clinically demonstrable remissions after surgical and radiological treatment (*Horst et al.* 153, 155, 157; *Blomfield et al.* 37; *Frecdberg et al.* 91, 92); and even in patients with post-surgical myxedema, high PBI^{131} values have been observed (*Blom et al.* 35). These findings can best be explained by the assumption that the remnant of gland is under increased thyrotropic stimulation and in reality is hyperactive, but that due to the small mass of active thyroid tissue the total hormone secretion will be normal or subnormal. It is accordingly evident that these tests (PBI^{131} , BEI^{131} , conversion ratio) are unsuitable as a means of studying changes in the thyroid function after therapy. As regards radioiodine treatment they are of interest mainly from two points of view. A rapid release of organic I^{131} from the gland may seriously influence the tests used for estimating the accumulation of I^{131} in the gland (for instance the 24 hours uptake). Secondly, the release of organic I^{131} modifies the irradiation dose in the thyroid after an administered therapeutic activity, so that both determination of the effective half-life (EHL) for I^{131} in the gland and studies of the blood level of I^{131} may serve as guidance in the choice of suitable therapeutic amounts.

In order to elucidate the frequency of this pathological type of radioiodine test, one group of treated patients with definite remissions after long-term observation was investigated in the following way.

Technique. — The uptake was measured 3 hours, 1 day, 2 days and 8 days after a tracer dose (60 microcuries I^{131}) given orally on an empty stomach. All measurements were done with the scintillation counter, and no correction for body background was made. After 48 hours, 25 ml venous blood was taken in a heparinized test tube. After separation of plasma and blood cells, 10 ml plasma was transferred to a 50 ml centrifugation tube. Ten ml of 20 per cent trichloroacetic acid was slowly added during careful mixing. After centrifugation the supernatant fluid was removed and the precipitate was washed with 10 per cent trichloroacetic acid and recentrifuged. The washing procedure was repeated twice. The precipitate was then dissolved in 5 ml 2.5-N NaOH and diluted to a volume of 10 ml with water and measured in the liquid counter as previously described in respect of total plasma. The technique is, in principle, the same as that previously described by *Goodwin et al.* (105). The sensitivity of this method is rather low, and in normal subjects scarcely more than detectable activities can usually be found. No conclusions have been drawn, however, from differences in this low range.

If the above-mentioned mechanism is correct, normal values of stable protein-bound iodine in the serum (SPI) must be expected even in cases where PBI^{131} is pathologically increased. The SPI was therefore determined concurrently in most of these cases. This investigation was carried out by Dr. G. Widström, using a technique described by *Barker et al.* (20, 21).

4. General Scheme of the Investigation

The present investigation had, with regard to the radioiodine tracer tests, two main aims:

A. To study the I^{131} -accumulating capacity of the gland before and at varying intervals after the treatment, in order to elucidate the correlation between that function and the clinical picture and to find what guidance the tracer tests might afford in the further management of the treatment. For this purpose most patients were studied by a simple tracer test (T_{24} and U_{24}), repeated at 2—4 months intervals during the first year after the treatment and then at longer intervals. In a small group of patients tracer tests were made earlier — 2—4 weeks after the treatment — in order to study the early changes in the I^{131} -collecting ability of the gland. Due to the high activity persisting in the gland after the therapeutic dose, only U_{24} was usually determined after the very early tracer tests.

B. To study any eventual pathological type of tracer tests in patients with remissions after I^{131} treatment, and to elucidate in what degree such a condition limits the diagnostic value of the tracer tests after the treatment. Three types of examinations were performed for this purpose:

(1). One group of patients with remissions after long-term observation were examined with respect to the 3 hours, 1, 2 and 8 days uptake in the thyroid, U_{24} , PBI^{131} after 48 hours, and SPI.

(2). Another group of patients, also with definite remissions after long observation, were examined after intravenous injection of the tracer dose and with continuous registration of the "neck curves" for the initial period after the injection, besides estimation of T_{24} and U_{24} .

(3). In one group of patients parallel estimations of the thyroid uptake curve and the plasma concentration curve were made after intravenous injection, in order to study the organic binding of I^{131} in the gland. In these patients the release of thyroid radioiodine after thiocyanate intake was also studied. The results of these investigations are reported in Chapter III.

Additional Technical Data. — As regards the therapeutic activities the standardization used at Harwell was employed.

After the therapeutic doses the 24-hours uptake and 24-hours urinary excretion were also measured; in one part of the series, only the 24-hours excretion. These values were usually in fairly good agreement with the results after the tracer tests; the series includes only a few cases with any major discrepancy, warranting the suspicion of excessive iodine intake between the tracer dose and the therapeutic dose.

When a tracer test was done within the first 2—3 months after the treatment, a correction often had to be made for remaining activity in the thyroid. Before the tracer dose was given, the activity in the thyroid was measured and expressed as percent of the standard tracer dose. If the persisting activity did not exceed 10 per cent of this tracer dose, the observed percentage was only subtracted from the measured 24-hours uptake, the biologic decay of the remaining I^{131} in the gland thus being ignored. The error introduced in this way was small, and even if the biologic half-life were so extremely short as 3 days and the remaining activity 10 per cent of the new tracer dose (which seldom occurred), the absolute error introduced by the correction should be only 2 per cent. If the remaining activity exceeded 10 per cent, the tracer dose was increased to a corresponding degree. The error in estimation of the urinary excretion was even smaller, as not all of the I^{131} released from the gland was excreted in the urine, but a substantial part in the feces.

In a small part of the series, even very early tracer tests were done (2—4 weeks). Due to the high activity in the thyroid, only U_{24} was estimated. For correction the urine was collected for 24 hours before the new tracer dose. The tracer dose given was so adjusted that the activity in the collected urine did not exceed 5 per cent of the dose. The measured 24-hours excretion after the tracer dose was then corrected simply by subtracting the percentage found in the urine during the foregoing 24 hours. Even if the biologic half-life of I^{131} in the gland were as short as 3 days and all the released I^{131} were excreted in the urine, the absolute error introduced would thus be less than one per cent.

CHAPTER II

Composition of the Series and Therapeutic Results

1. Introduction

The knowledge that the thyroid gland concentrates iodine, the experience that external irradiation treatment may bring about a remission of hyperthyroidism, and the production of serviceable radioactive iodine isotopes, constituted the immediate background of the radioiodine treatment of toxic goiter. The first patients were treated by *Hertz* and *Roberts* in 1941 (135, 137, 138), who used a mixture of I^{130} and I^{131} , in which the former constituted about 90 per cent of the initial activity. Somewhat later in 1941, *Hamilton* and *Soley* (cited in 126) treated their first cases with I^{131} . These early trials, and the continued work in the same clinics (*Chapman, Evans, Skanse et al.* 53, 54, 56—59, 198; *Soley, Miller et al.* 207, 209—211, 313—317), clearly demonstrated the efficacy of radioiodine in the treatment of hyperthyroidism, as has been verified by all other investigators too (*Werner, Quimby, Schmidt, Goodwin* 362, 364, 365, 368, 369; *Kelsey, Haines, Keating et al.* 122, 171, 172; *Williams et al.* 374—376; *Crile, McCullagh, Richards et al.* 69, 70, 192—194, 245, 266; *Johnson et al.* 165; *Prinzmetal et al.* 247, 248; *Freedberg et al.* 90, 96; *Moe et al.* 212; *Burrows et al.* 44; *Sweeney et al.* 331; *Hunt* 158; *Fietelberg et al.* 83; *Gordon et al.* 108; *Scott et al.* 294; *Hursh et al.* 159; *Abbatt et al.* 1; *Horst et al.* 151, 153, 155, 157; *Shipley et al.* 303; *Blomfield et al.* 36, 37, 356; *Seed et al.* 295, 296; *Weinbren* 361.)

2. Factors of Importance to the Result

Irradiation Dose. — The dosage problem associated with radioisotope therapy has been discussed by several authors (*Evans* 81, *Quimby* 249, *Marinelli, Quimby & Hine* 200, *Bush* 46, *Perry* 238, *Oddie* 226). The irradiation dose delivered to the thyroid gland during treatment with I^{131} is referable to both β and γ -radiation. If the isotope could be evenly distributed within the gland, the β dose would be quite homogeneous with the exception of a narrow zone in

the periphery of the gland, with a width equal to the maximal range of the β particles. The γ dose is dependent upon the geometry of the gland, and is usually higher in the central parts of the lobes than in the peripheral. In reality the isotope is never homogeneously distributed. It is taken up by the thyroid cells and then stored in the colloid, and even if the concentration of the isotope were equal in all the follicles, the short range of the β particles and the dimensions of the follicles would cause the thyroid cells to receive different irradiation doses (*Oddie 226*). Since, moreover, the uptake of radioiodine, even in diffuse toxic goiters, may be different in different follicles (*cf. Kelsey et al. 171*), it is obvious that the β dose is rather inhomogeneous. The γ radiation contributes only about 10 per cent (*Perry 238*) to the total absorbed energy, and the equalizing effect of this radiation on the dose distribution is of minor importance. That the distribution of the isotope in nodular goiters must be very irregular is already obvious from the anatomical conditions, and has also been studied in operation specimens (*Rawson, Skanse et al. 261, 262, Taylor 343*, and others) and by *in vivo* measurements with directional counters.

Despite the irregular distribution, the most rational basis for dosimetry in diffuse goiters would be the calculation of an "average β dose", *i.e.*, the β dose that would be obtained if the isotope were homogeneously distributed in the gland. This dose (D) can be expressed by the following formula:

$$D = \frac{\int_0^{\infty} A \, dt}{M} \cdot C_1 \dots\dots\dots (11)$$

where A is the activity of I^{131} in the gland, M the mass of the gland, t the time after administration, and C_1 a constant. Since A is a complicated function, the following approximation has often been used for calculation of the average dose:

$$D = C \cdot \frac{a \cdot T \cdot E}{M} \dots\dots\dots (12)$$

where a is the administered activity, T the percent of it taken up by the gland, and E the effective half-life for I^{131} in the thyroid. (If D is the average β dose in r.e.p., a is expressed in microcuries, E in days, and M in grams, the value of C will be about 0.18). Using this formula, the irradiation dose delivered to the thyroid before the time at which T is calculated is neglected, and it is also assumed that the I^{131} content of the gland after that time diminishes according to a simple exponential course. These approximations may constitute

substantial errors (*Miller and Sheline, 209*), which, however, are of minor importance compared with the errors in estimation of the uptake and, especially, the size of the gland.

Radiosensitivity. — Due to the difficulty of calculating the average dose, and above all the inhomogeneity of the dosage distribution, the influence of this factor can hardly be studied after radioiodine treatment. There is little doubt, however, that variations in radiosensitivity have an important bearing on the result. The tissue in the toxic goiters covers a wide range of functional levels, from the almost normal to the most extreme degree of cell activity; and variations in histologic picture, mitotic activity, etc. are certainly associated with differences in radiosensitivity. Experience of external irradiation treatment of toxic goiters revealed that the fastest results were obtained in the soft, diffusely enlarged glands, while nodular toxic goiters usually were treated with less success. — External irradiation treatment has also disclosed that normal thyroid tissue is much more radioresistant than hyperactive thyroid tissue. Doses used for diffuse toxic goiters never produce clinically detectable functional alterations in normal thyroids. It is also likely that the pronounced histologic changes caused by iodine treatment or thiouracil treatment are combined with changes in radiosensitivity. Iodine treatment causes involution and decreased cellular activity and should thus tend to diminish radiosensitivity. *Pfahler* (cited in 54) observed that the response to external irradiation treatment was poor when the patient had been previously treated with iodine. Thiouracil generally causes hyperplasia of the gland with increased mitotic activity, and should thus give a higher radiosensitivity; results of combined thiouracil and roentgen treatment may support this view (*Böe et al. 47*). It must be emphasized, however, that with exception of the well established difference between normal and hyperactive thyroid tissue, very little is known about variations in radiosensitivity in different types of thyroid tissue, or those caused by various drugs.

Most authors agree that the optimal average dose for treatment of diffuse toxic goiter with I^{131} has an order of magnitude of about 5,000—15,000 r.e.p. The impression is often gained that the diffuse toxic goiters, which rapidly diminish in size after treatment, are more radiosensitive than the nodular toxic goiters. This observation may, however, also be explained by the differing distribution of the isotope and the absence of degenerative changes, as fibrosis, etc. Unexpected results are often observed after radioiodine treatment.

Werner (362) noted for instance, in diffuse toxic goiters, myxedema in one case after an average dose of 2,900 r.e.p. and in other cases absence of response after more than 10,000 r.e.p. Such observations may have at least three explanations: namely, errors in the dose calculation, variations in distribution of the isotope, and, lastly, variations in radiosensitivity.

Radioiodine has also been used for destruction of the normal thyroid tissue in euthyroid cases with severe cardiac failure (*Freedberg, Blumgart et al.* 38—40, 89) and in cases with thyroid carcinoma metastases (*Rawson et al.* 256, *Seidlin et al.* 288); and average doses of the order of 25,000—75,000 r.e.p. have usually been necessary for complete functional ablation. The author (180) treated a series of euthyroid patients with congestive heart failure with smaller doses — roughly 10—20,000 r.e.p. — but only a minor proportion of the patients had definite myxedema, while in most cases only a transitory effect on the thyroid function was observed. Experience with radioiodine treatment thus supports the view that normal thyroid tissue is more radioresistant than hyperactive tissue.

Other Biological Factors. — Hyperthyroidism is sometimes a self-limiting disease, and spontaneous recovery or recovery under nonspecific treatment alone is well known. Some patients who were early treated with radioiodine (*Hertz and Roberts* 135, *Miller et al.* 209) before sufficient experience had been acquired, had remissions after astonishingly small doses. It seems likely that even a small inadequate dose may sometimes “help the patient to cure himself”. *Astwood* (14) drew, in this connection, a parallel with the treatment with antithyroid drugs, saying: “The question arises whether these small doses may not have produced a transient metabolic disorder in the thyroid without destroying it, and recovery from the hyperthyroidism took place during the interval when the thyroid’s function was thus temporarily disturbed.” That very small doses may sometimes produce temporary remission was demonstrated by *Werner et al.* (366). They administered small activities (0.04—0.2 mC I^{131}) once weekly for 3—6 weeks to patients with hyperthyroidism and noted in some cases transient remission.

On the other hand, there are also cases that seem to be unusually resistant to all therapy. In some cases hyperthyroidism recurs despite repeated operations and almost as long as there is still thyroid tissue left. The incidence of such cases is probably not high, but certainly higher in a series selected for radioiodine therapy than in an unselected series. The existence of these cases

may sometimes explain why a few patients, despite transient remissions, require a large number of treatments before definite remission occurs.

A factor of great importance to the result is probably the pituitary-thyroid interrelation. Many patients are euthyroid after the treatment, but the cause of this can scarcely be that the surviving thyroid tissue is just sufficient for normal hormone production. It is likely that, due to the pituitary-thyroid interrelation, an adaptation of the surviving thyroid tissue will occur, thus ensuring an adequate hormone production. *Werner et al.* (367) studied the effect of TSH and thyroid medication on the uptake of I^{131} in untreated exophthalmic goiters and radioiodine treated exophthalmic goiters in remission. In the untreated cases no effect was found, but in cases in remission the uptake increased after TSH and decreased after thyroid medication, indicating that the thyroid could be influenced by thyrotropic hormone. *Horst* (153, 155) conducted a similar investigation and obtained somewhat different results. In one group of patients with remission after radioiodine he found a similar response to that in normal individuals after TSH or thyroid administration. In another group he found no effect on the uptake after TSH and thyroid medication, and concluded that these cases probably did not have a normal pituitary-thyroid interrelation, and that the remnant of the gland stood under maximal stimulation by TSH, which was not influenced by the thyroid medication.

3. Practical Management of the Treatment

During the early therapeutic trials with both I^{130} and I^{131} , relatively small activities were used for obvious reasons (*Hertz and Roberts* 135, 137, *Soley, Miller et al.* 313, 314, 315). The dosimetric importance of the thyroid weight and the uptake of the isotope was early realized, and with increasing experience activities could be so chosen that a relatively large proportion of the cases had a remission after one or two treatments, without too high an incidence of hypothyroidism. Since then, the activity for an individual treatment has usually been selected according to one of the following principles.

1. A constant basic activity. (108).
2. An activity adapted to the weight of the thyroid. (209, 376, 331, 212).
3. An activity adapted to the weight of the thyroid and the uptake of the isotope in the gland. (59, 83, 217, 159).
4. An activity which, judging from the thyroid weight and the curve for

I^{131} in the thyroid after a preceding tracer test, will give a suitable average dose. (209, 364, 365, 36, 37, 44, 155).

The first method can hardly be used in series with goiters greatly varying in size, since it is impossible to choose an activity suitable for the small goiters which may produce remission in patients with large goiters within a reasonable time, even after multiple treatments. Methods 2 and 3 seem to be the most commonly used. In principle they differ but little, as most toxic goiters have an increased uptake of I^{131} without too large variations. For the exceptional cases in which treatment is given despite a low uptake, even those authors who use method 2 will probably adapt the administered activity to the amount of the uptake.

Theoretically, there is no doubt that method 4 is the most rational, for it takes into consideration not only variations in the size of the gland and the uptake, but also the variable disappearance rate of radioiodine in the thyroid. Some authors have used the method after a fairly complete study of the thyroid uptake curve, a method which approaches the use of the ideal formula (11) (*Miller and Sheline*, 209), but most have used the approximate formula (12). In this formula, T has usually been represented either by the "peak uptake" or by the uptake after a certain time, for instance 24 hours, or it has been determined indirectly from the urinary excretion. E has been determined after repeated measurements over the thyroid for several days, and M by clinical estimation of the size of the thyroid. The error in estimation of the uptake has previously been discussed, and it may, at least in cases with small or moderate goiters, be depressed to a level of no practical importance in the average dose calculation. E , too, may be determined with considerable accuracy, the more so in that the absolute magnitude of the uptake is of no importance in this estimation. In some cases the approximate formula (12) may include a substantial error due to the fact that the disappearance of I^{131} does not follow a simple exponential course (*Miller and Sheline*, 209), but the approximation seems justified for most cases.

The practical value of the average dose calculation is, however, marred by the discrepancy observed between the "preselected" dose, calculated from the tracer test, and the "delivered" dose calculated after administration of the therapeutic activity. *Miller and Sheline* (209) made in one series a careful comparison and found that the discrepancy was actually so large that, in their opinion, the time-consuming average dose calculation was not worth while. The results of treatment were quite as well, or better, correlated with the

administered activity per gram thyroid tissue, and the authors recommended this simpler dosimetry. Closer agreement was found in another series (*Blomfield et al.* 36), but there too the differences were sometimes striking. Estimation of the effective half-life is time-consuming and rather inconvenient in ambulatory practice. Cases with a short effective half-life of I^{131} in the thyroid also have high values of I^{131} in the plasma after 48 hours, and vice versa. *Rall et al.* (255) in one series where the administered activity had only been adapted to the size of the thyroid, found that the frequency of remissions was lower, on the average, in the cases that showed high plasma concentrations of I^{131} after 48 hours, probably due to the more rapid disappearance of the isotope from the thyroid in those cases. For the calculation of a suitable therapeutic activity they suggested the use of a formula which, besides the weight of the gland and the uptake, also included the plasma concentrations of I^{131} after 48 hours.

Estimation of the thyroid size is associated with serious errors. Three methods may afford information about this size: palpation, roentgen examination, and the delineation of some projection of the gland with a directional counter after I^{131} administration. *Soley* (315) determined the thyroid weight by palpation in 74 cases before thyroidectomy: in 25 per cent of the cases the error was less than 10 per cent, while in the other cases errors up to 40 per cent occurred. In a similar investigation by *Williams* (375) the accuracy was astonishingly good, possibly because the patients had readily palpable glands (most cases were thiouracil treated diffuse goiters). The error in clinical estimation is bound to be large in many cases with small glands, glands difficult to palpate, and recurrences after previous operations. Roentgen examination is useful for estimation of the thyroid size only in cases with intrathoracic goiters. With G.-M. counters or scintillation counters provided with suitable collimators, "scanning" of the activities in the neck may be performed and an idea obtained of the size of the thyroid. Due to the lower gamma-sensitivity of G.-M. counters, the scintillation counter is a great advance in this respect (*Allen, Bauer, Cassen et al.* 5, 6, 7, 8, 25, 48, 104). By outlining of the frontal silhouette with a directional counter, and the use of a simple formula, it has been found that the thyroid volume can be estimated with an average error of only 10 per cent (*Allen et al.* 5—7). Having regard to the major anatomical variations in the shape of the thyroid this degree of accuracy seems, however, to be somewhat too high (*Kelly* 170). In order to study the errors due to anatomical variations, 42 autopsy cases were examined (*Himanka and Lars-*

son, 146). The volume of the glands had a linear correlation to the expression $0.33 (\sqrt{A})^3$, where A is the area of the frontal projection. The average error when the volume was calculated from this area was, however, 20 per cent, and individual errors of up to 40 per cent were observed. In a pathologic series including thyroids of highly atypical shape (for instance, recurrences after previous operations), the errors will probably be even greater. Even with these objections, outlining of the thyroid with a directional scintillation counter is a definite advance for estimation of the size of the thyroid, at least in cases where the gland is difficult or impossible to palpate. For such cases it has been used in this series since May, 1953, and has often yielded valuable information.

In this series a rather simple dosimetry was used. In a large proportion of the cases, the size of the goiter could be clinically estimated only with very large errors (small or impalpable glands, recurrences after operation), and it is the author's opinion that both expression of the dose in mC per gram thyroid tissue and calculation of an average dose in r.e.p. would have given a false impression of the accuracy of the dosimetry. Patients with small or normal thyroid volumes (impalpable glands, recurrences without palpable goiter) were usually given 2—5 mC; slightly enlarged glands (30—50 grams) about 5—7 mC; moderately enlarged glands (50—100 grams) 7—10 mC; and large diffuse goiters (more than 100 grams) 10—20 mC. For the treatment of toxic nodular goiters, initial activities of 7—25 mC were usually given, depending on the size of the goiter. With increasing experience the dosage scheme was more individualized, with initial activities varying from 2 to 100 mC, the smallest activity being used for patients with very small glands and the largest for patients with very large nodular goiters. If the uptake in the thyroid, judging from the external measurement and the urinary excretion, was pathologically increased, no consideration was given to the size of the uptake when determining the activity to be administered. In a few cases, in which the uptake was low despite undoubted hyperthyroidism, the activity was increased in a corresponding degree.

Retreatment was not given, as a rule, until about two months after the first treatment. If the patient at that time was still hyperthyroid and had an increased uptake of I^{131} in the thyroid, a further therapeutic dose was administered.

Other factors, too, influenced the choice of the activity to be administered. In elderly subjects or in subjects with severe cardiac complications, rapid remission was considered more urgent than avoidance of hypothyroidism, and

a higher activity was often given. In patients with pronounced ocular symptoms, in whom a slow depression of the thyroid function was regarded as preferable, treatment with smaller doses, repeated every second month until a remission was brought about, was often preferred.

4. Composition of the Series

Indications for Treatment. — Radioiodine may bring about a remission in most cases with hyperthyroidism, but there is still some controversy about the indications for the treatment. Some clinics treat only the exceptional cases in which no other method can be used; others treat almost all cases regardless of age and type of goiter. Most authors have a more moderate opinion, but agree that radioiodine treatment should be used only on special indications. There are several reasons for this restrictive use. Subtotal thyroidectomy brings about, in most cases, a prompt remission. The potential danger inherent in radioiodine therapy (carcinogenesis, genetical disturbances) cannot be ignored, even though they are as yet hypothetical in man. Toxic nodular goiters diminish in size but do not disappear after radioiodine treatment, wherefore surgery is superior both from the cosmetic point of view and as regards the elimination of pressure symptoms. A nodular goiter may also contain a carcinoma that would be removed by surgery but would remain undetected after radioiodine treatment. The author had no part in the selection of patients in this series, but the more generally accepted indications are briefly summarized.

Absolute contraindication: Pregnancy after the fourteenth week, as the fetal thyroid begins to collect iodine at that time (*Chapman et al.* 55). Pregnant women in the first months have been treated with radioiodine both intentionally (*Chapman et al.* 57, 59) and unintentionally (*Clever* 64) without demonstrable damage to the fetus. It seems wise, however, to avoid I^{131} treatment during the whole of pregnancy.

Relative contraindications: Younger patients. Nodular goiters.

Absolute indication: Inoperable cases in which other methods have failed to bring about remission.

Relative indications: Older patients. Recurrences after subtotal thyroidectomy. Severe complicating diseases. Poor response to preoperative treatment. Recurrences after intensive roentgen treatment. Small goiters.

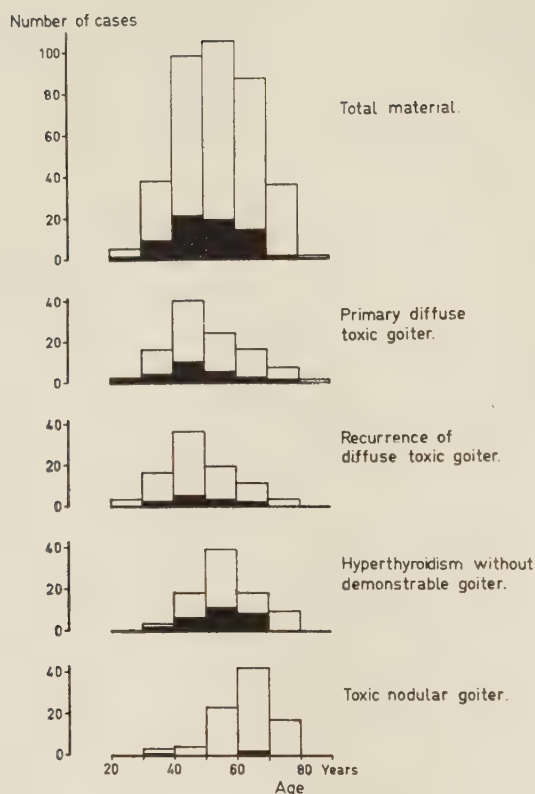


Fig. 12. Age distribution in the total series and the different types of goiters. Black columns: males. White columns: females.

Age, sex, type of goiter. For the following study all cases treated from 1951 to 1953 were selected, *i.e.* cases observed 1—4 years after the start of treatment. The series contained 305 females and 65 males with an age distribution illustrated in Fig. 12. Only 43 patients were under 40 years and only 5 under 30 years. No patient under the age of 20 years was treated, and 124 (33.5 per cent) were 60 years or more.

As regards the type of goiter the series was divided into the following groups:

1. Primary diffuse toxic goiter 106 cases
2. Recurrent hyperthyroidism after thyroidectomy for diffuse toxic goiter 88 cases
3. Primary hyperthyroidism without demonstrable goiter 87 cases
4. Toxic nodular goiter 89 cases

The third of these groups is, of course, an artificial one from the anatomical point of view and includes cases in which the palpatory findings were normal and roentgen examination had not revealed intrathoracic goiters. The group is relatively large, due partly to the fact that a small thyroid was regarded as a special indication for the treatment (*Wijnblad*) and partly to the fact that this type of hyperthyroidism is relatively common in older subjects.

Complicating Diseases. — Cardiovascular diseases (including thyrocardiacs) were recorded in 155 patients. Of these, 57 had auricular fibrillation at the start of treatment and 10 had histories of intermittent or paroxysmal auricular fibrillation; 33 of the patients had signs of cardiac decompensation when the treatment started. Cardiac complications were most frequent in the group with nodular goiters, where 34 patients had auricular fibrillation. Other complicating diseases of importance to the indications were: diabetes in 11 cases, rheumatoid arthritis in 9, bronchial asthma in 3, parkinsonism in 3, mental diseases or senility in 17, uncontrolled or recently treated malignant diseases in 5, and acromegaly in one. Two patients had skin diseases with iodine allergy (Besnier's prurigo and herpetiform dermatitis), so that preoperative iodine treatment had to be avoided.

Previous Medical Treatment. — Treatment with thiouracil derivatives had been given in 149 cases. In 43 of these cases there had been a good response to the treatment but recurrence of hyperthyroidism after cessation of long-term treatment. In 19 cases the medication was discontinued because of toxic side-effects. In 58 cases the therapeutic response had been unsatisfactory. In the remaining 29 cases the thiouracil treatment had been only of short duration, and probably was not intended as definitive treatment.

Twenty-five patients had, during the last year, received iodine treatment for hyperthyroidism (16 of them had also been under thiouracil treatment, and are included in the above-mentioned group). Two of the patients had undergone operation less than a year before radioiodine treatment and had received preoperative iodine treatment. Three patients had been treated for thyrotoxic crisis before radioiodine treatment. In 15 cases preoperative iodine treatment had been given but, due to a poor response, the operation was not performed. In the last 5 cases iodine treatment was given without any operation being intended; in two of the cases very severe hyperthyroidism with threatening crisis was the indication for the treatment.

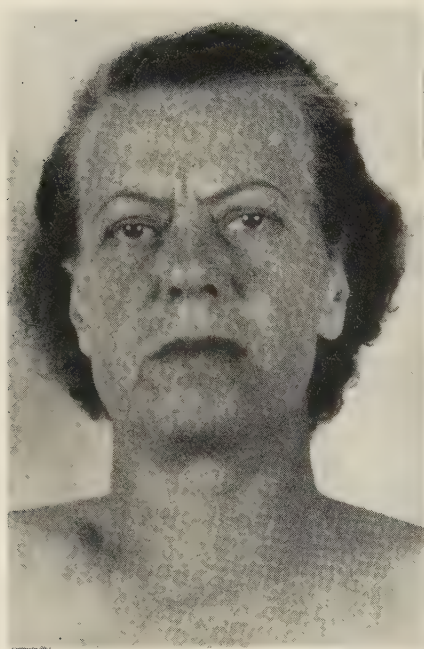


Fig. 13 a.

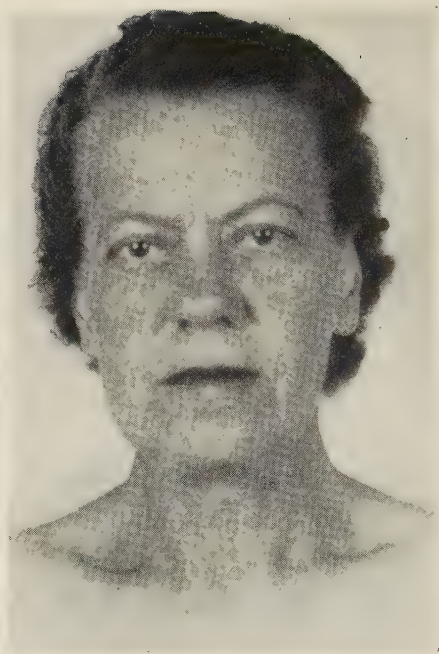


Fig. 13 b.

Figs. 13 a, b and c. *EML. R. 7449/52.* Woman, 49, with longstanding exophthalmic goiter; in May 1952 admitted to a hospital for thyrotoxic crisis, auricular fibrillation and cardiac decompensation. After treatment with iodine and propylthiouracil she improved and was able

Combination of Radioiodine with Other Specific Agents. — The clinical course after a single treatment with radioiodine varies. A few patients already feel some relief in the first few days, and continue to improve during the following weeks. More commonly the improvement does not begin for 3—6 weeks. Lastly, there are cases in which the first treatment is quite inadequate, with complete absence of remission. More or less severe exacerbations of the thyrotoxic symptoms during the first few weeks after the treatment were early observed in some cases (*Soley et al. 317*) and have since been verified in all major series. Even cases with fatal crisis after the treatment have been reported (*Nelson et al. 223; Feitelberg et al. 83*).

The first cases to be treated with radioactive iodine (*Hertz and Roberts, 135*) received conventional iodine treatment during the first few weeks after radioiodine administration, since it was realized that only relatively slowly could the irradiation treatment bring about a remission. As the combined treat-

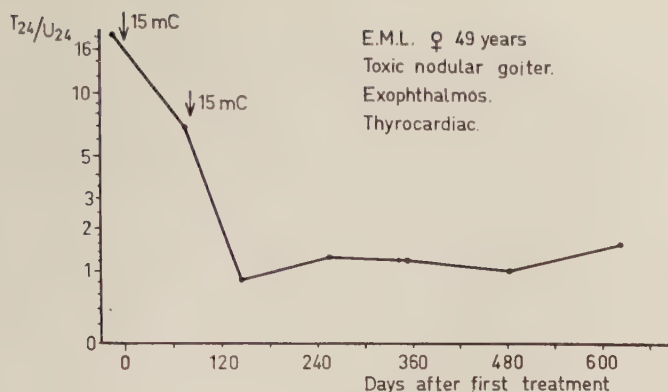


Fig. 13 c.

to continue on propylthiouracil alone. Due to an exacerbation she again received iodine for a time in Aug. 1952, followed by propylthiouracil alone — first 400 mg daily, then a gradual reduction to 250 mg daily, and withdrawal on Nov. 3, 1952 for tracer test and radioiodine treatment. The tracer test (Nov. 5) revealed T_{24} 69 per cent and U_{24} 4 per cent. She was in a severe thyrotoxic state, with moderate exophthalmos, auricular fibrillation and signs of cardiac decompensation. Her thyroid was generally enlarged with a nodular character, and on Nov. 20 she received 15 mC I^{131} . After a transient improvement she deteriorated again, with increased signs of hyperthyroidism and cardiac decompensation; and a new tracer test on Feb. 4, 1953 revealed T_{24} 62 per cent and U_{24} 9 per cent. She received a further 15 mC I^{131} on Feb. 12 and improved rapidly after this treatment: since about 2 months after the treatment, there have been no signs of hyperthyroidism. The goiter can no longer be palpated; she has a regular pulse and no signs of decompensation. Repeated tracer tests have revealed an uptake of 30–44 per cent, and the SPI in Feb. 1955 was 4.6 gamma. A. Appearance before treatment. B. April 14, 1953. C. Result of tracer tests.

ment made evaluation of the result more difficult, later investigators (*Chapman and Evans*, 56) treated their patients with radioiodine alone, and in most cases the course was uncomplicated. Since then, most authors have avoided, in the majority of the cases, any specific pre- or post-treatment. There is, however, a small group of patients in whom radioiodine cannot be used as the only specific agent, or can be used only with certain risks, namely:

1. Cases with thyrotoxic crisis.
2. Cases with very severe hyperthyroidism and threatening crisis.
3. Cases with severe hyperthyroidism and serious complicating diseases.

That the first group must be treated in the conventional way with iodine needs no comment. If radioiodine in such cases is the alternative for definite treatment, it will be ideal if iodine can be gradually exchanged for thiouracil and the latter continued for a sufficient time until the effect of iodine on the uptake has disappeared. In this series three patients had been treated for

thyrotoxic crisis during the last year before radioiodine treatment. In two of these, the above-mentioned scheme could be followed and both cases were treated with radioiodine with good results. One of these cases is illustrated in Fig. 13. The patient was a 49-year-old woman with long-standing exophthalmic goiter and was admitted to a medical department with thyrotoxic crisis and cardiac decompensation. After treatment with iodine and propylthiouracil followed by propylthiouracil alone, she was improved but still hyperthyroid, and was then treated with radioiodine with a complete remission.

If the patient shows toxic side-reactions to thiouracil and rapidly deteriorates as soon as iodine is discontinued, a difficult problem may occur if radioiodine is the only alternative for definite treatment. This is illustrated by the third of these cases, which had recently been treated for thyrotoxic crisis.

LLS. R. 5804/53 Man, aged 66, previously treated for cardiosclerosis, hypertension and cardiac decompensation and, in April 1953, admitted to a medical department for increasing thyrotoxic symptoms. He had no palpable goiter and no ocular signs but a definite picture of hyperthyroidism; and a few days after admission a thyrotoxic crisis developed. He improved after iodine and propylthiouracil treatment but at the beginning of June he had severe leukopenia, with a drop in the white cell count to 700, so that thiouracil was discontinued. Despite iodine he had a high pulse rate and high B.M.R., and was also considered inoperable due to his poor general condition. For planned radioiodine treatment, the iodine was gradually diminished and discontinued on August 25, 1953. Tracer test on Sept. 7, 1953 revealed $T_{24} = 8$ per cent and $U_{24} = 60$ per cent, and radioiodine treatment was regarded as impossible. Subsequently he continued to receive nonspecific treatment only, but gradually deteriorated, and when the next tracer test was performed on Oct. 14, 1953 he had beginning thyrotoxic crisis. T_{24} was 13 per cent; examination by directional counter revealed a small thyroid; urinary collection was incomplete due to his confused mental state. As it seemed impossible to wait longer without iodine he received, on Oct. 15, 50 mC I^{131} intravenously, followed after 24 hours by massive iodine treatment. Due to his poor condition no measurements were done for the first few days, but after 5 days his thyroid still contained about 1.5 mC. The ensuing period was critical, with high pulse rate, fever, mental confusion and circulatory insufficiency. Under continued iodine treatment and treatment of the circulatory insufficiency he nevertheless improved and, on Oct. 24, could be sent back to his hospital. Iodine was then gradually diminished and discontinued in the middle of Dec. 1953 without deterioration. He was in fairly good condition for a couple of months but died suddenly on March 12, 1954, with a dissecting aortic aneurysm as the immediate cause of death and severe general arteriosclerosis. The thyroid was small, each lobe had the size of an almond, and had a fibrotic gross appearance on section. Microscopic examination revealed extensive fibrosis, and the thyroid was also fixed to the trachea with fibrotic tissue. It contained scattered medium-sized follicles with cuboid or low epithelium and a few microcysts.

In view of the high activity administered and the small thyroid volume, it is possible that this patient received an adequate irradiation dose despite

the low uptake. Iodine could also be discontinued without the rapid deterioration previously observed. He died from a complicating disease, and the extensive fibrosis observed in his thyroid may be consistent with an irradiation effect.

Fortunately the effect of iodine on the uptake of radioiodine disappears more rapidly in most cases of hyperthyroidism. *Chapman and Evans* (57) observed that the effect often disappeared after 2—3 weeks, in contrast to euthyroid cases, where the effect may be very long-standing. The same observation was made in this series. There was, however, considerable variability. The series includes cases in which the uptake was already pathologically increased 3—6 days after cessation of iodine treatment, but also cases where the uptake was depressed several months after iodine treatment. Besides the reported case LLS the series contained, however, only three cases in which previous iodine treatment caused a delay of the radioiodine treatment; and as these cases had relatively slight hyperthyroidism this delay was of little practical importance. The author has since observed one patient with severe hyperthyroidism in whom radioiodine treatment has so far been impossible due to previous iodine medication. As this state appears to be the only technical hindrance to radioiodine treatment, the case is briefly reported:

SP. A. 7220/54 Woman, 65, with nodular goiter since her youth. Since the spring of 1954, increasing hyperthyroidism; B.M.R. at the end of May, + 77 per cent. She received preoperative Lugol treatment from June 15 to July 21, without improvement. B.M.R. on July 19, + 77 and + 79 per cent. From July she received thiouracil without benefit, and from Sept. 6 to Oct. 6, again Lugol treatment intended as preoperative. Still no improvement; high pulse rate; B.M.R. on Oct. 5, + 83 per cent. Iodine was discontinued and she was sent for radioiodine treatment. All tracer tests hitherto performed have revealed a low uptake:

	T_{24}	U_{24}
Oct. 25, 1954	10	80
Nov. 30, 1954	4	61
Jan. 31, 1955	7	62
Feb. 14, 1955	8	58
Feb. 21, 1955	6	63

The last two tracer tests were done after propylthiouracil treatment since Feb. 2, and each time discontinued 2 days before the tracer test. The patient refuses iodine medication since the Lugol treatment. She has a large nodular goiter weighing more than 150 g, severe hyperthyroidism with high pulse rate, and of late, auricular fibrillation. Due to the low uptake radioiodine treatment has up to now (4 months after Lugol treatment) been impossible, and she is continuing on thiouracil in the hope that the iodine effect on the uptake will sooner or later disappear.

For the small proportion of cases, *i.e.*, patients with very severe hyperthyroidism or serious complicating diseases, in which the slow response and occurrence of exacerbations makes radioiodine treatment alone too hazardous, it is obvious that thiouracil is the ideal agent for pretreatment. *Skanse* (310) investigated the effect of thiouracil on the uptake of I^{131} in thyrotoxic patients, and found a depression during treatment but a rapid return to pretreatment level after cessation, and 2—4 days withdrawal was usually sufficient. *Chapman, Skanse and Evans* (59) suggested the possibility of combining radioiodine with thiouracil in problem cases, and it has since been used and recommended by several authors (*Williams et al.* 375, 376; *McCullagh et al.* 194; *Sweeney et al.* 331; *Hunt* 158; *Abbatt et al.* 1; *Horst et al.* 157). In one series (*Abbatt et al.* 1) 70 cases were treated consistently with thiouracil during one period both before and after radioiodine treatment, and the authors concluded that the post-treatment course was more uncomplicated than could have been expected after radioiodine alone; they also found that the biologic half-life of I^{131} in thyroid was less variable, which facilitated the average dose calculation. *Hamilton and Werner* (123) studied for physiologic purposes the influence of iodide, propylthiouracil and tapazole administered during a 2-weeks period, starting one week after radioiodine treatment. They found that with iodide and tapazole the improvement began at an earlier stage than was expected after radioiodine alone. Nevertheless there are many reasons for avoiding a combination of radioiodine and other specific agents in the majority of cases. The effect is more easily evaluated after simple treatment and, during the post-treatment course, iodine at least will reduce the value of subsequent tracer tests, which otherwise constitute valuable guidance for the continued treatment. In most cases with fairly severe hyperthyroidism and complicating diseases, it also seems sufficient to combine radioiodine with careful nonspecific treatment and control of the complicating diseases. The simplicity of radioiodine treatment in this respect may generally be regarded as an advantage compared with surgical treatment, where the specific pretreatment not infrequently constitutes a difficult problem (*cf. Wijnblad*, 372).

In this series many patients had received thiouracil, but only in a few was it really intended as pretreatment for radioiodine. In Fig. 14 a case is illustrated where the combined treatment probably was necessary. The patient was a man, 24 years old, with diabetes of juvenile type controlled for several years with insulin. After rapidly developing exophthalmic goiter, he had a severe exacerbation of his diabetes and was in a precomatous condition. He improved



Fig. 14 a.



Fig. 14 b.

Figs. 14 a and b. *G.S.A. R. 6814/51*. Man, 24, with diabetes detected in 1940 and controlled with insulin. In Aug. 1951 admitted to a hospital with a severe exacerbation of the diabetes and in a precomatous condition. Simultaneously, typical Grave's disease was discovered, with diffuse goiter, ocular symptoms and B.M.R. +73 per cent. After adjustment of insulin and treatment of the hyperthyroidism with diiodotyrosine and propylthiouracil, he improved but at no time was free from thyrotoxic symptoms. Diiodotyrosine and thiouracil were discontinued on Nov. 21, 1951, and from Nov. 29 until Dec. 1 he received roentgen treatment with 3×100 r to the thyroid. Only a few days after withdrawal of the medication, there was a rapid deterioration with increasing pulse rate, fever and threatening crisis and simultaneously the diabetes exacerbated. Roentgen treatment was stopped but propylthiouracil continued, and he improved gradually. He was, however, still hyperthyroid; B.M.R. on June 9, 1952, +41 per cent. Propylthiouracil was discontinued on June 8, 1952; a tracer test on June 11 revealed a high uptake, and he received 10 mC I^{131} . One day after radioiodine treatment propylthiouracil was continued, the first few weeks with 150 mg daily, the next two weeks 100 mg daily, and a further two weeks 50 mg daily before cessation. The post-treatment course was uneventful. The thyrotoxic symptoms disappeared during the first 2—3 months; he regained normal weight and his goiter was no longer palpable. The diabetes has been easily controlled and it has been possible to reduce the dose of insulin. He has remained euthyroid since the treatment. A. Before radioiodine treatment B. May 18, 1953.

after iodine and thiouracil but was still thyrotoxic, and only a few days withdrawal of the medication provoked a rapid deterioration with threatening crisis and also exacerbation of the diabetes. After continued propylthiouracil medication, cessation of the drug 2 days before a tracer test, and radioiodine treat-

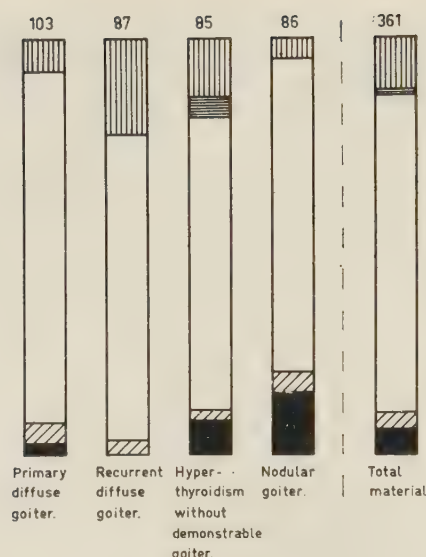


Fig. 15. End results in the total series and the different groups of goiters. The figures above each column represent the number of cases in each group. Columns with vertical lines: hypothyroid cases requiring substitution therapy. Columns with transverse lines: patients in whom the hypothyroidism was induced because of congestive heart failure. White columns: euthyroid. Columns with oblique lines: still hyperthyroid or re-treated since Oct. 1, 1954. Black columns: deaths during the observation period.

ment and continued propylthiouracil in gradually diminishing doses during the first six weeks, the course was uncomplicated and a good end result was obtained.

5. Results of Treatment

The total series treated from 1951 to 1953 comprised 370 cases, in 361 of which the results of treatment could be analyzed. The results are summarized in Table 1 and graphically illustrated in Fig. 15. Two hundred and seventy-six patients (76 per cent) were euthyroid or most probably euthyroid at the end of the observation period. Forty-eight cases (13 per cent) had hypothyroidism requiring substitution therapy. In 4 of these cases hypothyroidism was intentionally caused, due to congestive heart failure. Fourteen cases (4 per cent) were still hyperthyroid or recently re-treated. Twenty-three patients had died during the observation period, and the causes of death will be analyzed later.

In Fig. 16 the results after varying times (6, 12, 18 and 24 months) from the start of treatment are shown. Patients re-treated less than 2 months before the end of each observation period were classified as still thyrotoxic.

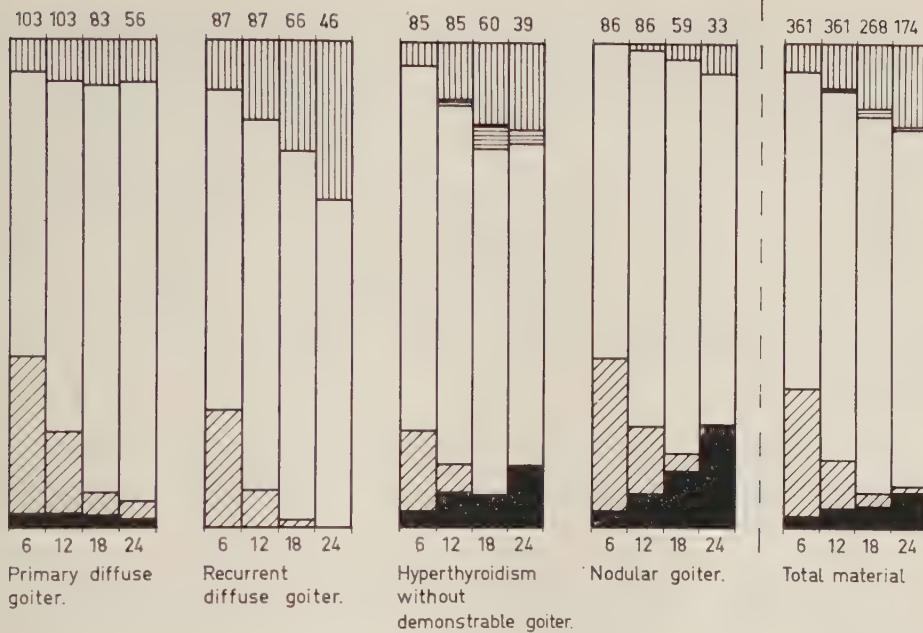


Fig. 16. Results of treatment after varying periods. The figures below the columns signify the number of months after the start of treatment; those above the columns, the number of cases observed. The columns with oblique lines refer to patients still hyperthyroid or re-treated less than two months before the end of the observation period. Other columns as in Fig. 4.

Table 1. Results of treatment

	Primary diffuse goiter	Recurrent diffuse goiter	Primary hyperthyroidism without demonstrable goiter	Nodular goiter	Total series
Total number of cases	103	87	85	86	361
A. Hypothyroidism	8	20	16	4	48
B. Euthyroid	85	61	51	54	251
C. Estimation difficult, probably euthyroid	2	3	9	11	25
Patients with remission (A, B and C), last treatment given before July 1, 1954	93	83	75	67	318
D. Thyrotoxic	5	3	2	4	14
Dead during the observation period	3	0	7	13	23

Nine cases were excluded from the analysis of the results. Two of them were operated on within a few months after radioiodine treatment: one for persistent hyperthyroidism and one for removal of a nodular goiter. Seven patients were incompletely followed up; they were alive at the end of the observation period but had not presented themselves for follow-up examination.

The other patients were all carefully followed up, usually by both the surgeon or physician who had referred the patient for treatment, and at Radiumhemmet. Besides the clinical examination, tracer tests were done on repeated occasions. The B.M.R. and serum cholesterol were in some cases followed consistently; in others they were only determined sporadically as a complement to the clinical picture. The S.P.I. was used partly for a special investigation reported in Chapter III and partly in cases in which the classification was questionable. All patients were followed up until the end of 1954 or the beginning of 1955. They were assigned to the different groups in Table I according to the following principles:

- a. Hypothyroid. All patients requiring substitution therapy.
- b. Euthyroid. All patients with undoubted remissions who did not require substitution. Patients with very slight hypothyroidism not requiring substitution were also assigned to this group.
- c. Estimation difficult, probably euthyroid. All cases in which evaluation of the thyroid function was difficult due to severe complicating diseases or for other reasons, but in which prolonged clinical observation and the laboratory tests made it most probable that remission had occurred.
- d. Thyrotoxic. All cases with undoubted persisting hyperthyroidism, and also all cases that most probably were thyrotoxic. All cases re-treated after Oct. 1, 1954 were also assigned to this group, whether later examination had revealed persisting hyperthyroidism or not.

In all the graphic illustrations of the results, groups b and c have been combined.

The lowest initial activity administered was 1 mC and the highest 100 mC. The lowest total activity was 2 mC and the highest 150 mC. The average number of treatments was $622/361 = 1.72$. One hundred and ninety cases received one treatment; 110, two treatments; 40, three treatments; 14, four treatments; 6, five treatments; and one patient received six treatments.

Primary Diffuse Toxic Goiter. — This group comprised 103 cases in which the results could be analyzed. Of these, 87 (84 per cent) were euthyroid at the end of the observation period. Eight cases (8 per cent) had hypothyroidism requiring substitution therapy, five were still thyrotoxic or recently re-treated, and three patients had died.

The group included 55 cases in which the thyroid was recorded as slightly enlarged (probably less than 50 g), 40 in which it was moderately enlarged, and 8 with large goiters (probably weighing more than 100 g). In the following table some data concerning the treatment in these subgroups are given.

Size of goiter	<i>Small</i>	<i>Moderate</i>	<i>Large</i>
Number of cases	55 (44)	40 (36)	8 (7)
Still toxic or recently re-treated	2	2	1
Average number of treatments	1.55 (1.50)	2.03 (1.94)	2.63 (2.29)
Remission after one treatment	64 %	52.5 %	0 %
Hypothyroidism	11 %	5 %	0 %
Average initial activity (mC) ..	5.3 (5.4)	6.7 (6.7)	14.1 (13.9)
Average total activity (mC) ..	7.4 (7.3)	13.5 (11.8)	34.6 (31.9)

(The figures in parentheses refer only to patients who were alive and euthyroid at the end of the observation period.)

The average number of treatments thus increased and the incidence of hypothyroidism decreased with increasing size of the goiter. A possible explanation may be that the administered initial activities were not, on the average, proportional to the size of the goiter. The mean values in the above table may, however, convey a somewhat false impression of the correlation between the size of the goiter and the activity required. The individual variations were in this respect extremely large, as may be demonstrated by some examples. The group with slightly enlarged thyroids included one case that was euthyroid after a single treatment with 2 mC, and one case that was still toxic after four treatments with a total of 16 mC. The group with moderately enlarged glands included one case that was euthyroid after 4 mC and one case that was still hyperthyroid after four treatments with a total of 51 mC. One of the patients with large goiters was euthyroid after two treatments with a total of 16 mC, and one patient not until four treatments with a total of 73 mC.

Six cases in the group with small goiters became hypothyroid. Four of them had received a single treatment (4—6 mC with an average of 4.75 mC) and two of them two treatments (6+5 and 7+4 mC). Two cases with moderately enlarged goiters became hypothyroid, each of them after a single treatment (6 and 7 mC).

The four cases in Figs. 17—20 have been selected as examples. Fig. 17 demonstrates an uncomplicated case with an ideal response to a single treatment. The goiter diminished rapidly during the first two months and, after a period with slight transient hypothyroidism, the patient remained euthyroid. Fig. 18 shows a patient with a very large diffuse goiter. The goiter diminished rapidly after the first treatment but there was still pronounced hyperthyroidism two months later, and a definite remission did not set in until the second treatment

had been given. The patients in Figs. 19 and 20 were both problem cases. The first patient was not operable after iodine treatment and developed leukopenia after thiouracil. She was severely toxic when the treatment started; emaciated and with auricular fibrillation; the goiter was small and hard (iodine involution). After the first treatment there was a transient exacerbation of the hyperthyroid symptoms and increased cardiac decompensation, but she then rapidly improved and was, after a total of three treatments, greatly improved and had gained 24 kg in weight. The last case (Fig. 20) had, despite pre-operative iodine treatment, gradually deteriorated and after thiouracil she had severe leukopenia. When radioiodine therapy started she was in an extreme thyrotoxic state, with threatening crisis. She had a fairly large diffuse goiter and received initially 10 mC I^{131} . Despite a decrease of the goiter her condition deteriorated, with gradual weight loss and development of pronounced thyrotoxic myopathy. She was still unimproved after a second treatment, but improved rapidly after a third one and showed a definite remission after a fourth treatment, having received a total of 73 mC. Despite the critical condition after the first treatment, she received no iodine, partly because of the previous poor response and partly due to the risk of delaying further radioiodine treatment. The last-named patient demonstrates how complicated and critical the post-treatment course may be in some cases.

Concurrently with the functional remission, diffuse goiters usually diminish rapidly in size, with return of normal palpatory findings. This was already observed by the first investigators (*Hertz and Roberts*, 135) and has been verified by all later investigators. This course is so common that there is often reason to question whether a remission really has occurred, if the thyroid is still enlarged. Exceptions have, however, been reported. *Hertz and Roberts* (138) observed a few cases in which a small, dense remnant of the goiter persisted despite functional remission. The iodine treatment invariably given by these authors may, however, have influenced the palpatory findings; but similar observations have been made by later investigators without concomitant iodine treatment. *Shipley et al.* (303) described cases of diffuse goiter in which small nodules could be palpated when the main part of the goiter had disappeared after radioiodine treatment. *Lindsay et al.* (186) made anatomical examinations of 24 radioiodine treated diffuse goiters (autopsy or operation material) and found in two of them multiple adenomas. It is possible that after the subtotal destruction of the thyroid a nodular regeneration may occur, perhaps from parts of the gland which have received less irradiation. Another

explanation may be that a goiter, clinically classified as diffuse, may from the outset have concealed small adenomas, which are more palpable when the goiter shrinks after radioiodine treatment. In this series the palpatory findings were recorded as normal after treatment in 86 of 103 cases. Two patients had died within the first half year after treatment and could not be evaluated. In 12 patients the thyroid had considerably diminished but was still slightly enlarged; two of these patients were still thyrotoxic. One patient had a small, dense diffuse goiter that was more or less unchanged in size despite functional remission, and in two patients small nodules were later palpated, in both cases being detected about two years after the start of treatment. The decrease in size of diffuse goiters in connection with the treatment is illustrated in Figs. 14, 17, 18 and 20.

Recurrent Hyperthyroidism after Operation for Diffuse Toxic Goiter. — This group comprised 87 cases in which the results could be analyzed. Seven patients had been operated on twice or more; eight had recurrent nerve paralysis; one had tetany, and eleven had received roentgen treatment.

In this group 64 cases (73.5 per cent) were euthyroid, 20 patients (23 per cent) had hypothyroidism requiring substitution therapy, and three patients were greatly improved but still thyrotoxic and recently re-treated.

The group contained 31 cases in which no recurrence of the goiter could be palpated, and 56 cases with palpable recurrences. Three patients had very large nodular recurrences. In the following table these three cases have been referred to a separate group.

Goiter	Not palpable	Palpable recurrence	Very large nodular goiter
Number of cases	31 (20)	53 (41)	3 (3)
Still toxic or recently re-treated	0	3	0
Average number of treatments	1.45 (1.50)	1.79 (1.85)	2
Remission after one treatment	61 %	45 %	33 %
Hypothyroidism	35.5 %	17 %	0
Average initial activity (mC) ..	4.4 (4.4)	5.4 (5.0)	18 (18)
Average total activity (mC) ..	6.2 (6.3)	10.4 (10.8)	49.5 (49.5)

(The figures in parentheses refer only to patients who were alive and euthyroid at the end of the observation period.)

The incidence of hypothyroidism was higher in this than in any other group in the series, and it was very high in the cases without palpable recurrences.



Fig. 17 a.



Fig. 17 b.



Fig. 18 a.



Fig. 18 b.

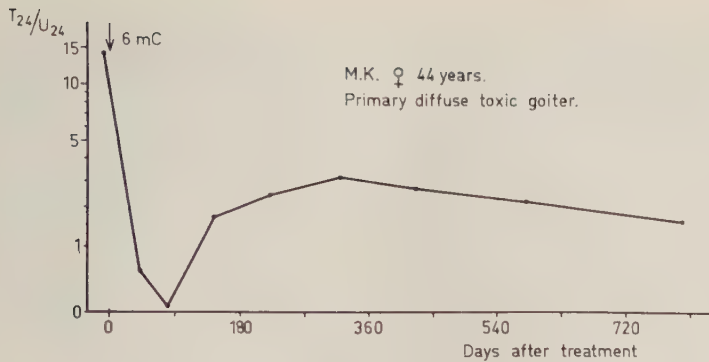


Fig. 17 c.

Figs. 17 a, b and c. *M.K.* R. 5497/52. Woman, 44, with diffuse toxic goiter. Rapid disappearance of the goiter after a single treatment with 6 mC I^{131} on Aug. 20, 1952. From Nov. 1952 to Feb. 1953, slight signs of hypothyroidism, but later euthyroid. A. Before treatment. B. March 31, 1953. C. Result of tracer tests.

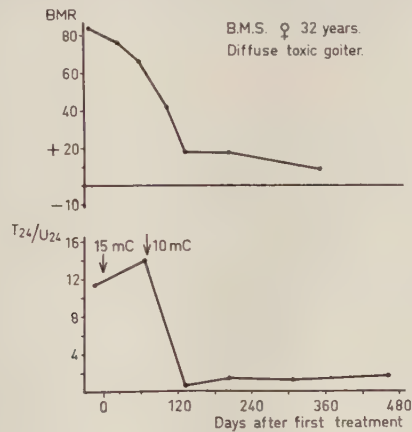


Fig. 18 c.

Figs. 18 a, b and c. *B.M.S.* R. 2750/53. Woman, 32, with exophthalmic goiter since 1946. Admitted to surgical department in 1946 and 1950, but refused operation. After Dec. 1952 she rapidly deteriorated and, in Feb. 1953, was again admitted for surgical treatment. She received preoperative iodine treatment Feb. 9 to March 7, 1953, with a poor response. The B.M.R. decreased from +81 to +48, but the pulse rate was high and operation out of the question. Iodine was gradually exchanged for propylthiouracil, but despite an increase of the doses up to 500 mg daily she still had pronounced hyperthyroidism, and the B.M.R. on April 14, 1953 was +84 per cent. Thiouracil was withdrawn on April 15, and a tracer test on April 22 revealed T_{24} 68 per cent and U_{24} 6 per cent. She had a large diffuse goiter, pronounced hyperthyroidism and exophthalmus, and received on May 7, 15 mC I^{131} . The goiter diminished rapidly in size but she still had conspicuous signs of hyperthyroidism; a tracer test on July 13 revealed T_{24} 70 per cent and U_{24} 5 per cent, and she received further treatment with 10 mC I^{131} . After this treatment there was a definite remission, with disappearance of the goiter and the hyperthyroid symptoms. She was still euthyroid at the last follow-up in Feb. 1955. A. Before treatment. B. Sept. 14, 1953. C. B.M.R. and tracer tests.



Fig. 19 a.

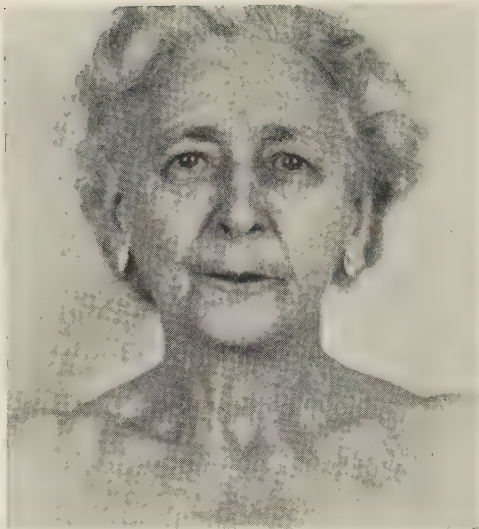


Fig. 19 b.

Figs. 19 a and b. *ITL*. R. 7796/52. Woman, 63, with exophthalmic goiter since 1949. Lugol therapy in 1949 with good effect, but not operated on. After propylthiouracil there was leukopenia, and after roentgen treatment only a transient improvement. She again received preoperative Lugol treatment in March 1950, but with a poor response, and after a further trial of propylthiouracil there was severe leukopenia. She was now sent for radioiodine treatment. Tracer test on Nov. 19, 1952 revealed T_{24} 81 per cent and U_{24} 5 per cent. She had pronounced hyperthyroidism; B.M.R. +60; serum cholesterol 106 mg %; weight 42.5 Kg. Auricular fibrillation. The goiter was small and hard (probably iodine involution), and she received on Nov. 20, 6.5 mC I^{131} . From Nov. 23 she had a transient exacerbation with increased hyperthyroidism and cardiac decompensation, but later improved rapidly. She was still hyperthyroid in March 1953, and after a tracer test on March 25, which revealed T_{24} 64 per cent and U_{24} 7 per cent, she received 5 mC I^{131} on March 27. She was further improved but still toxic on Oct. 28, 1953; T_{24} 62 per cent, U_{24} 16 per cent; and received 4 mC I^{131} on Nov. 2, 1953. The pulse was already regularized after the first treatment. She has increased in weight from 42.5 to 66 Kg. The B.M.R. has fallen from +60 to +8, and the serum cholesterol increased from 106 to 332. Last tracer test on Jan. 26, 1955 revealed T_{24} 49 per cent and U_{24} 33 per cent. A. Before radioiodine treatment. B. Feb. 5, 1954.

These cases probably received, on the average, too high activities in relation to the volume of the thyroid tissue. Overdosage was most common in the early treated cases, and it will later be shown that the incidence of hypothyroidism was greatly reduced with increasing experience. As in the primary diffuse goiters there were, however, many instances of an unexpected therapeutic response. One patient with a very small palpable recurrence, also outlined by directional scintillation counter and probably not weighing more than about

15 g, did not become euthyroid until three treatments with a total of 63 mC had been given. Another patient with a somewhat larger thyroid volume, judging from the scintigram, developed myxedema after 3 mC.

In the group without palpable recurrences, 11 had hypothyroidism. In 7 cases the hypothyroidism already appeared after the first treatment (3—6 mC with an average of 4.4 mC), and in 4 cases after two treatments (initial activity 3—5 mC; total activity 7—12 mC; average 4.5 and 8.8 respectively).

Of the patients with palpable recurrences, 9 showed hypothyroidism. Seven of them had received a single treatment (2 of them had small recurrences and had received 4 and 5 mC; 3 had moderately large goiters and had received 6, 7 and 8 mC; 2 had large diffuse recurrences and had received 15 mC). Two cases with fairly small recurrences of the goiter showed hypothyroidism after 2 treatments (6+7 and 5+3 mC).

Figs. 21—24 demonstrate four examples from this group. The first patient (Fig. 21) was an uncomplicated case with a symmetrical diffuse recurrence. The goiter disappeared rapidly during the first 2 months after a single treatment, and the patient remained euthyroid. The second patient (Fig. 22) was also an uncomplicated case with a symmetrical diffuse recurrence of about the same size. She was treated with multiple relatively low activities, with gradual improvement and remission. The next case (Fig. 23) was a severely incapacitated cardiac patient (combined aortic and mitral valvular disease), in whom the heart symptoms had for many years masked the recurrent hyperthyroidism. The result of radioiodine treatment was excellent, but despite a very small recurrence she required three treatments with a total of 63 mC before remission occurred. The last two treatments were actually calculated to produce myxedema, but the end result was nevertheless a euthyroid patient.

The aforementioned three patients with very large nodular recurrences were good examples of absolute indications for radioiodine treatment. They had all been operated on twice, had received roentgen treatment in several series and had skin atrophy and telangiectases. All had large multinodular goiters fixed in fibrotic tissue, and two of them had recurrent nerve paralysis. One had leukopenia after thiouracil, one recurrent hyperthyroidism after prolonged thiouracil treatment, and one had shown a poor therapeutic response to thiouracil. They received 25, 30 and 94 mC, divided into one, two and three treatments respectively. In two of them the therapeutic results were very good and demonstrable remissions occurred. The third patient is difficult to evaluate due to metastasizing breast carcinoma and poor general condition. However,



Fig. 20 a.

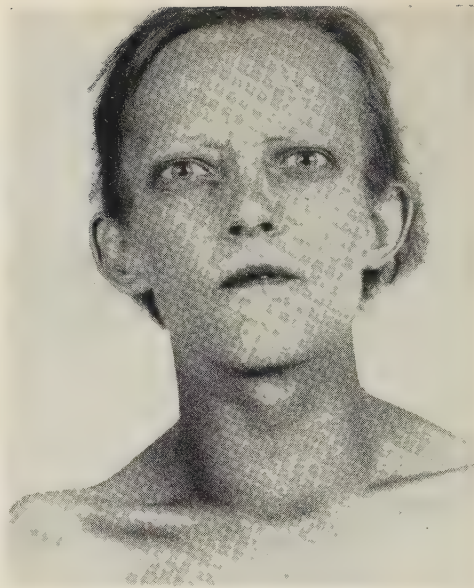


Fig. 20 b.

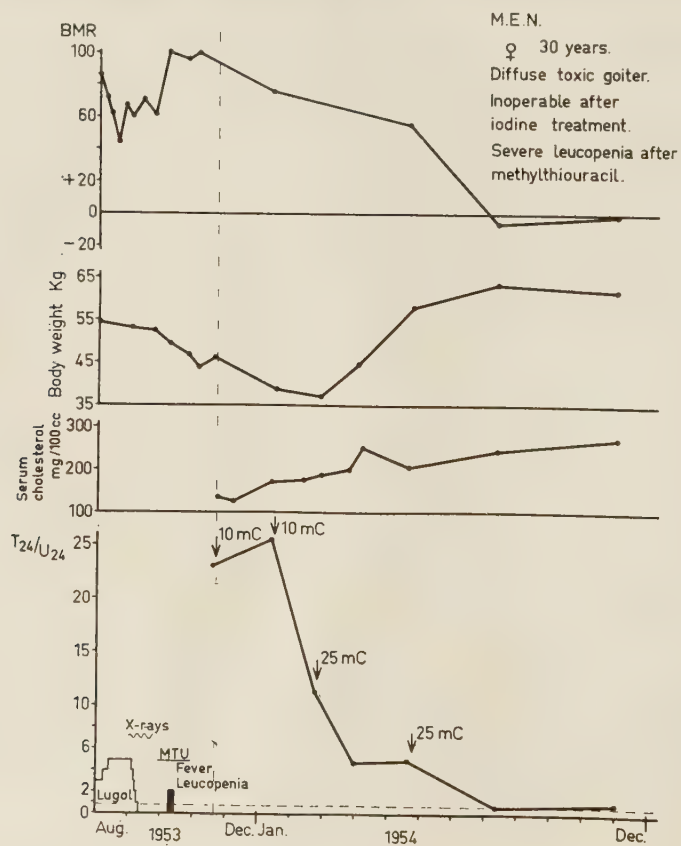


Fig. 20 e.

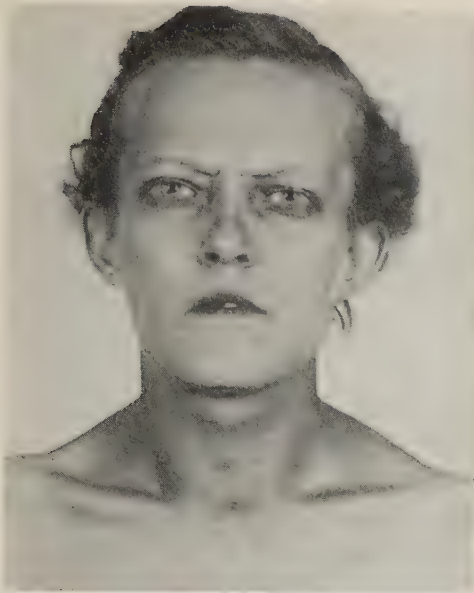


Fig. 20 c.



Fig. 20 d.

Figs. 20 a, b, c and d. *MEN*. R. 7795/53. Woman, 30, with exophthalmic goiter since 1949. She was treated with methylthiouracil for half a year with a good response, but showed an almost immediate recurrence after cessation in Nov. 1949. Methylthiouracil was again instituted as from Jan. 1950, with good effect, and withdrawn in Nov. 1951. From June 1953, recurrence of hyperthyroidism; B.M.R. +63 per cent. Thiouracil was not tried because of leukopenia, and on July 30, 1953 she was admitted to a surgical department for operation. Despite preoperative iodine treatment she gradually deteriorated and operation was not possible. Roentgen treatment was given in the beginning of Sept. 1953, without improvement, and after a few days treatment with methylthiouracil the white blood cell count dropped to 700. Throughout hospitalization she had pronounced anemia (Hb 40—50 per cent) that was resistant to treatment. Before radioiodine treatment she was in a severe thyrotoxic state, with high pulse rate (110—120), high B.M.R. subfebrile. Hb 52 per cent; R.B.C. 2.7 million; W.B.C. 4,000. Sternal puncture revealed hyperplastic bone marrow, in contrast to the peripheral blood picture. Tracer test on Nov. 16: T_{24} 69 per cent. U_{24} 3 per cent. She had a large diffuse goiter and on Nov. 20 received 10 mC I^{131} . Despite a gradual decrease of the goiter, her condition progressively deteriorated, with weight loss, high pulse rate, and gradually developing thyrotoxic myopathy with severe muscular atrophy of the shoulder girdle; during one period she could not voluntarily raise her arms from the bed. As the uptake of I^{131} was still high she received further radioiodine treatments on Jan. 14 and Feb. 22, 1954. She was unimproved after the second treatment but improved gradually after the third one and, on April 5, was able to leave the hospital. She had, during the whole period, pronounced anemia (Hb 40—60 per cent; R.B.C. 2.5—3.5 million), resistant to all treatment (iron, liver preparation, B_{12} , folic acid). Despite the severe thyrotoxic state she received, aside from radioiodine, only nonspecific treatment (blood transfusions, testosterone, sedatives). When seen again on May 18, 1954 she was definitely improved but still hyperthyroid; pulse rate 90—100. Tracer test: T_{24} 54 per cent, U_{24} 11 per cent. Her thyroid was still slightly enlarged and she received 25 mC I^{131} . After this treatment there was a rapid improvement, with disappearance of all signs of hyperthyroidism and without signs of hypothyroidism. At the last follow-up in Dec. 1954, she was still in excellent condition and euthyroid. The anemia, previously resistant to all treatment, subsided with remission of the hyperthyroidism. Hb 88 per cent; R.B.C. 4.5 million. Slight persisting leukopenia; last white cell count 3,000. A. Before treatment. B. March 3, 1954. C. April 5, 1954. D. Dec. 2, 1954. E. Results of laboratory tests.

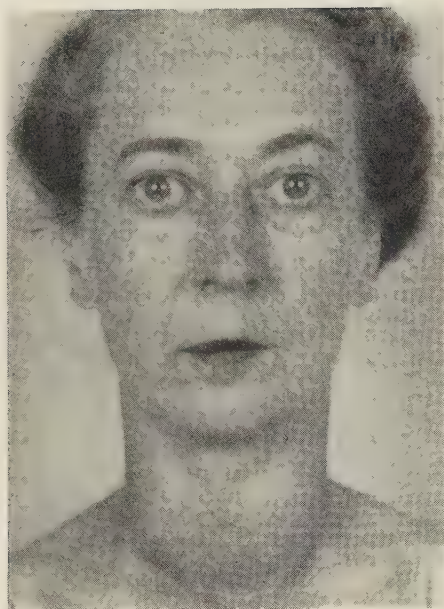


Fig. 21 a.



Fig. 21 b.

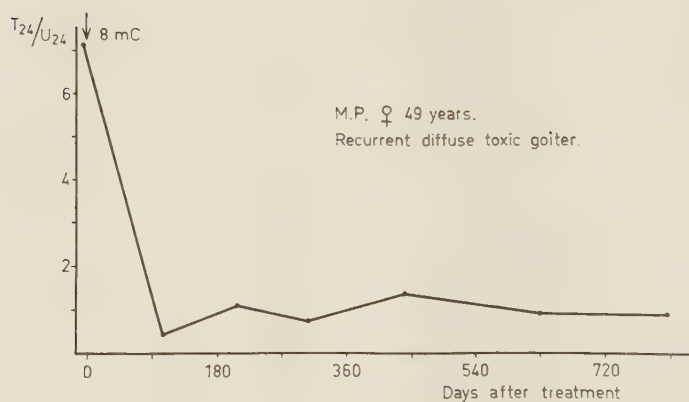


Fig. 21 c.

Figs. 21 a, b and c. *MP. R. 4476/52.* Woman, 49, operated on 15 years before for exophthalmic goiter. Recurrent hyperthyroidism since 1945, treated by methylthiouracil with a relatively good response but with exacerbation after cessation. She had a definite picture of hyperthyroidism and a diffuse soft recurrence of the goiter. After treatment with 8 mC I^{131} on July 2, 1952, uncomplicated course with rapid disappearance of the goiter in about 2–3 months; and since that time also euthyroid. A. Before treatment. B. Sept. 16, 1954. C. Results of tracer tests.

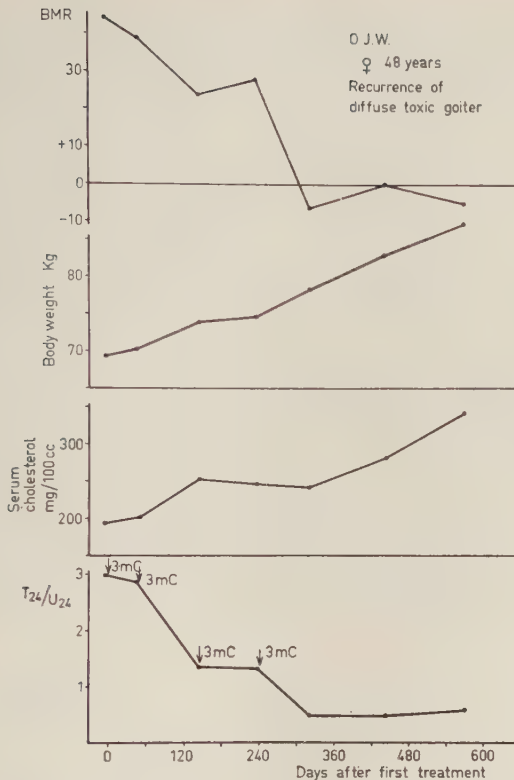


Fig. 22. *CJW*. R.2076/53. Woman, 48, operated on in May 1951, for diffuse toxic goiter. Recurrent hyperthyroidism of half a year's standing and also increasing recurrence of the goiter. On admission on March 30, 1953, moderate hyperthyroidism and a bilateral diffuse recurrence of the goiter (50–60 g). After a total of four treatments with 3 mC each, repeated every second to third month as long as she still had signs of hyperthyroidism and increased uptake of I^{131} in the thyroid, she gradually improved and has been euthyroid since about 2 months after the last treatment. The goiter gradually became impalpable.

both the clinical findings and the laboratory tests make it highly probable that remission of hyperthyroidism has occurred. One of these cases is demonstrated in Fig. 24 as an example.

The behavior of the goiter varied more in this group than in the primary diffuse goiters. In patients with diffuse soft recurrences, there was usually complete clinical resolution (Fig. 21), while in cases with nodular recurrences remnants of the goiter could often be palpated. The large nodular recurrences behaved like the other nodular goiters, i.e., diminished in size but considerable

remnants persisted (Fig. 24). In 30 cases with recurrences of diffuse type there was complete clinical resolution of the goiter in 25 cases. Of 26 cases with recurrences of nodular type the palpatory findings returned to normal only in ten.

Primary Hyperthyroidism without Demonstrable Goiter. — The series included 85 cases of this type in which the results of treatment could be analyzed. Of these, 60 (71 per cent) were euthyroid at the end of the observation period; 16 (19 per cent) had hypothyroidism; two were still toxic, and 7 had died during the observation period. In 4 of the 16 cases with hypothyroidism, this was intentionally caused because of congestive heart failure; and if these cases are excluded the incidence of hypothyroidism will be 14 per cent. It was thus higher than that in the primary diffuse goiters and the nodular goiters, but not as high as that in the recurrent diffuse goiters.

In the following table the four cases with intentionally provoked myxedema, and also the aforementioned patient in whom the treatment, due to a very low uptake, was highly atypical (LLS) are excluded.

Number of cases	80 (60)
Average number of treatments	1.44 (1.47)
Remission after one treatment	64 per cent
Hypothyroidism	15 per cent
Average initial activity (mC)	4.9 (4.7)
Average total activity (mC)	6.7 (6.5)

(The figures in parentheses refer only to patients who were alive and euthyroid at the end of the observation period.)

No patient in this group required more than three treatments, and the highest total activity given for remission was 19 mC, divided into three treatments. The two patients recorded as still thyrotoxic were greatly improved after a single treatment, but recent follow-ups revealed slight persisting hyperthyroidism, wherefore they received additional treatment.

Of the 12 cases with "unintentional" hypothyroidism, 8 had received a single treatment (3—7.5 mC with an average of 5.4 mC) and 4 had received two treatments (4—6 mC initially and 7—11 mC totally). The four cases with "intentional" hypothyroidism were all euthyroid after previous radioiodine treatment, and received high additional activities (25—30 mC) which produced myxedema.

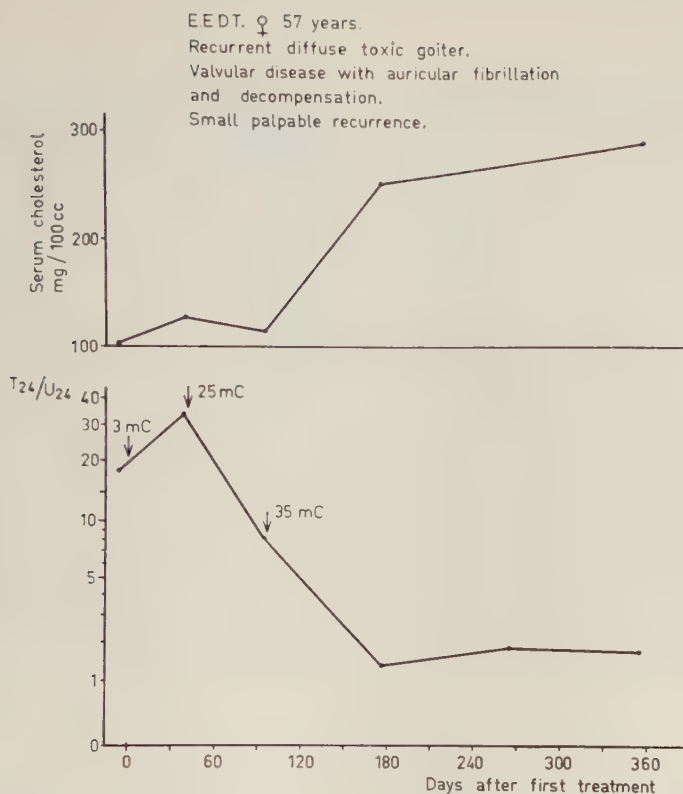


Fig. 23. EEDT. R. 7691/53. Woman, 57, operated on for exophthalmic goiter in 1930. In 1944 cardiac failure was detected (combined aortic and mitral valvular disease) together with auricular fibrillation. The B.M.R. was high and she received roentgen treatment to the thyroid. In the last two years she had been largely incapacitated, with long periods of cardiac decompensation; the last few months, permanent decompensation with edema, pleural transudation and liver swelling, despite adequate heart therapy. During hospitalization in Nov. 1953 hyperthyroidism was suspected; she was nervous, had sweats, was severely emaciated, and had decreased from 75 to 58 Kg in weight. She showed pronounced cardiac decompensation and a roentgenologic heart volume of 1,270 ml, pulmonary congestion and copious transudate in the left pleura. A tracer test on Nov. 11, 1953 revealed T_{24} 72 per cent and U_{24} 4 per cent. On the right side of the neck a small hard nodular recurrence was palpated, with a weight of about 15 g; and examination by directional scintillation counter revealed that the uptake was restricted to the palpated nodule. EHL, measured from 1 to 8 days, was 5 days, and she received 3 mC I^{131} (corresponding to an average dose of about 15,000 rep). Her condition was unimproved; a tracer test on Dec. 28 revealed T_{24} 82 per cent and U_{24} 2.4 per cent, and she then received 25 mC, intended to produce myxedema. She was still unimproved and hyperthyroid at the end of Feb. 1954. T_{24} 72 per cent and U_{24} 9 per cent. The palpated small recurrence was more or less unchanged in size, and she then received 35 mC I^{131} . After 6—8 weeks a progressive improvement set in; at a follow-up in May 1954 she was in excellent condition and had increased in weight to 69 Kg. The signs of cardiac decompensation had disappeared. She has since been in good condition and has resumed work, 7 hours daily. She still has auricular fibrillation but no signs of decompensation, and has been maintained on about the same dose of digitalis throughout the observation period. Despite the high activities given, she has no signs of hypothyroidism. In Nov. 1954, SPI 6.3, T_{24} 51 per cent; U_{24} 29 per cent.

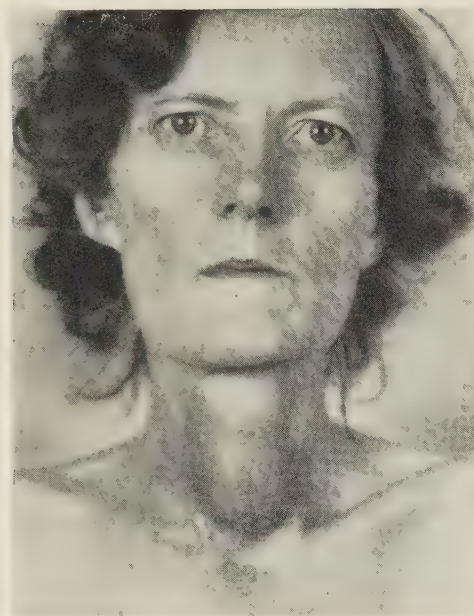


Fig. 24 a.



Fig. 24 b.

Figs. 24 a, b and c. *GMG. R. 8442/53.* Woman, 48, operated on in 1926 and 1951 for toxic goiter and with paralysis of right recurrent nerve. No remission since the last operation, and growing recurrence of the goiter. Roentgen treatment given without definite improvement. During the last year, auricular fibrillation and increasing heart symptoms. Propylthiouracil given without improvement, and withdrawn at the beginning of Nov. 1953. Before radioiodine treatment she had pronounced hyperthyroidism and a very large nodular goiter, fixed in fibrotic tissue; the skin of the neck was slightly atrophic with telangiectasis. After a tracer test with $T_{24} = 60$ per cent and $U_{24} = 10$ per cent, she received 25 mC I^{131} on Dec. 17, 1953. After the treatment there was a progressive improvement, and she has been euthyroid since Feb. 1954. She has a regular pulse and the ECG has been normalized. The roentgenographic heart volume diminished from 550 to 420 ml/sq.m. The patient has herself discontinued digitalis medication, which she found unnecessary. The goiter has diminished but a rather large remnant persists. A. Before treatment. B. Sept. 28, 1954. C. Laboratory tests.

It was previously mentioned that older subjects were often treated with somewhat higher activities in order to bring about remission as soon as possible. Nevertheless, hypothyroidism was commoner in the younger than in the older subjects. In the following table, both patients who died during the observation period and the four cases with intentional hypothyroidism are excluded.

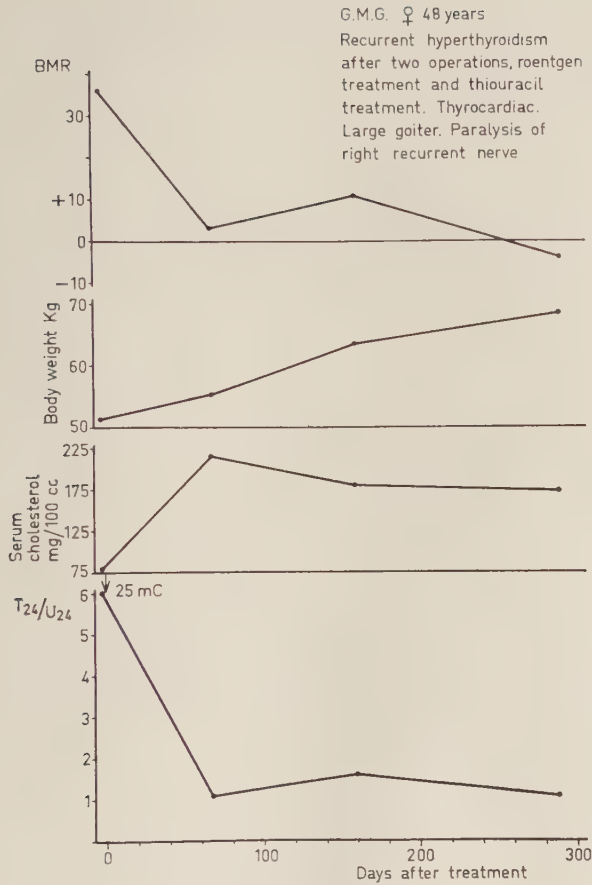


Fig. 24 c.

Age	Less than 60 years	60 years or over
Number of cases	53	21
Hypothyroidism	11 (21 %)	1 (5 %)
Average number of treatments ..	1.32	1.76
Average initial activity	4.7	5.0
Average total activity	5.7	8.0

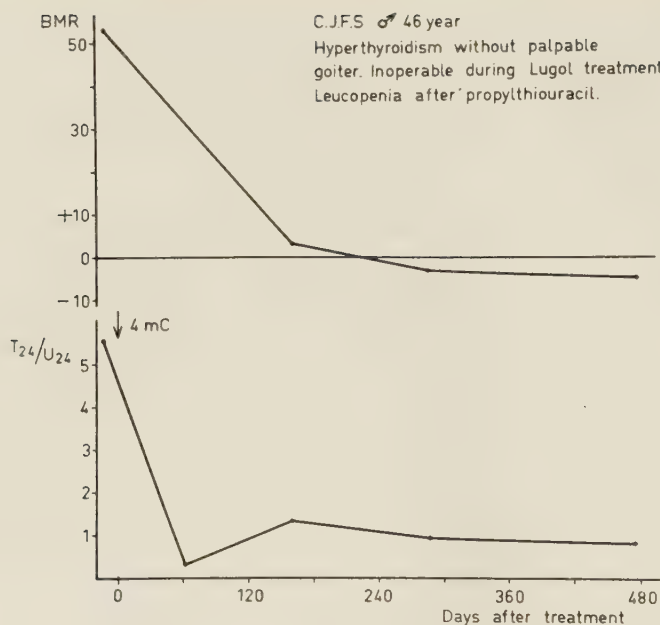


Fig. 25. C.J.F.S. R. 6176/52. Man, 46, with hyperthyroidism since 1947. The first few years, treated only by nonspecific agents. Since Feb. 1952, rapid deterioration; B.M.R. +40. Received preoperative iodine treatment for four weeks in Feb. 1952, but due to poor response the operation was not performed. Thereafter propylthiouracil, which soon had to be withdrawn because of leukopenia. B.M.R. in Sept. 1952, +53 per cent. He had typical signs of moderate hyperthyroidism, without ocular symptoms or palpable goiter. Tracer test on Sept. 11, 1952: T_{24} 75 per cent, U_{24} 13.5 per cent. Received 4 mC I^{131} on Sept. 25, 1952, with rapid improvement, and has been euthyroid since Nov. 1952.

The older subjects thus required, on the average, higher activities for remission, and hypothyroidism was unusual. The group is, of course, too small for definite conclusions, but the difference seems striking. There may be several explanations. The older subjects perhaps had, on the average, somewhat larger goiters, or this group may include more nodular goiters with irregular distribution of the isotope. Yet there may be, of course, a real difference in radio-sensitivity between goiters in younger and older patients.

In Figs. 25 and 26 two examples are given from this group. The first patient (Fig. 25) was a man who was considered inoperable after iodine treatment and had leukopenia after propylthiouracil. After a single radioiodine treatment he rapidly improved, and has been euthyroid since about 2 months after the treatment. The next patient (Fig. 26) was a woman with very severe hyper-

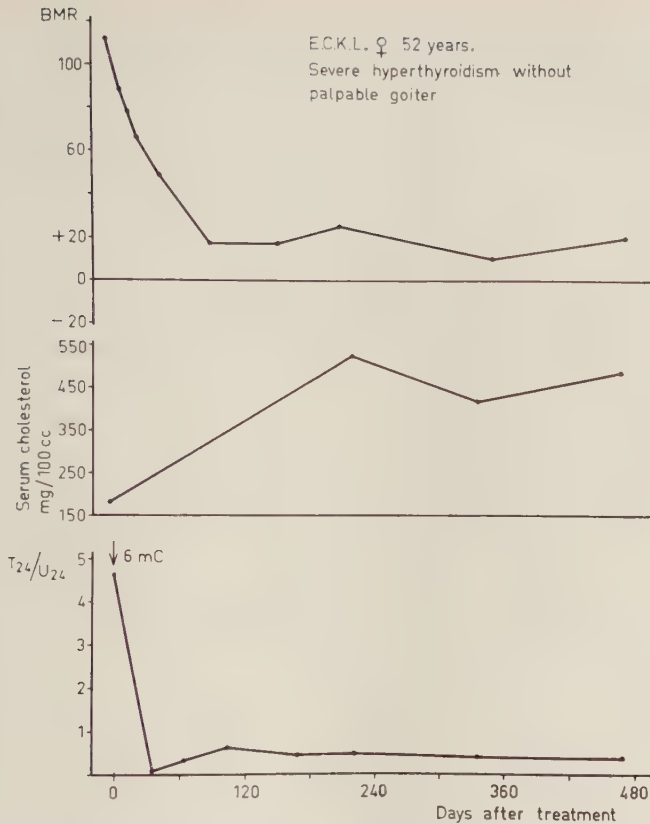


Fig. 26. ECKL. R. 6930/53. Woman, 52, with hyperthyroidism since the spring of 1953. Severe exacerbation since Sept. 1953, with very high pulse rate, B.M.R. +112, threatening crisis and psychotic symptoms. Stare, but no exophthalmos. No palpable goiter. Tracer test on Oct. 14, 1953: T_{24} 65 per cent; U_{24} 14 per cent. She received 6 mC I^{131} on Oct. 15, 1953, followed by a very rapid improvement, and has been euthyroid since the end of Nov. 1954. Since the treatment she has had high serum cholesterol values (Jan. 29, 1955, 487 mg %) and rather low uptake (T_{24} 22 per cent, U_{24} 57 per cent), but as yet no clinical signs of hypothyroidism.

thyroidism, threatening crisis and psychotic symptoms. Aside from radioiodine she received only nonspecific treatment and was kept under careful supervision in a medical department. There was a very rapid response to a single radioiodine treatment, and she was already clinically euthyroid 6—8 weeks after the treatment.

Toxic Nodular Goiter. — The indications for radioiodine treatment in this type of goiter may seem questionable. Both the possibility of the goiter containing a carcinoma and the fact that the goiter does not disappear after radio-

iodine treatment, despite functional remission, argue against the use of radioiodine in these cases. *Maloof and Chapman* (198) treated with radioiodine one case in which an operation, shortly afterwards, revealed a papillary carcinoma; and this experience led them to caution against the more general use of radioiodine for the treatment of nodular goiters. Toxic nodular goiters are, however, more common in older subjects and the patients often have severe cardiac complications. In view of the carcinoma risk too, a considerable number of these patients probably should never be operated on. The incidence of carcinoma is not very high, according to available statistics. *Beahrs, Pemberton and Black* (26) found in one series of 2,229 surgically treated toxic nodular goiters a carcinoma incidence of 1.2 per cent; and *Cole, Majarakis and Slaughter* (65), in a series of 378 cases, had an incidence of 1 per cent. In most reported series of surgically treated atoxic nodular goiters (*cf. Cole et al.* 65) the incidence of carcinoma is considerably higher, often 4—10 per cent. A possible explanation of this is that a relatively greater proportion of atoxic goiter cases are operated on because they present signs suggestive of malignancy (rapidly growing goiter, pressure symptoms), while toxic nodular goiter cases are operated on for the hyperthyroidism. Having regard to the peculiar biology of malignant thyroid growths, it is naturally impossible to know, moreover, how many of these "histological" carcinomas really would have developed into "clinical" carcinomas.

The early series treated by radioiodine consisted almost exclusively of diffuse toxic goiters. Large goiters were even regarded as a contraindication to radioiodine treatment (*Hertz and Roberts*, 138), mainly because of the high activities that would have been necessary for remission. Many later series include, however, a considerable number of nodular goiters (375, 69, 70, 192—194, 245, 212, 331, 62, 83, 108, 158). One report (*Richards et al.* 266) dealt solely with radioiodine treatment of toxic nodular goiters, with analysis of a series of 37 cases. It has been a general experience that this type of goiter requires relatively high activities for remission, and also that the incidence of hypothyroidism after treatment is low.

The present series contained 86 toxic nodular goiters in which the results of treatment could be analyzed. Sixty-five patients (76 per cent) were euthyroid or most probably euthyroid, at the end of the observation period, and four patients (5 per cent) had hypothyroidism requiring substitution therapy. Four patients were improved but still hyperthyroid and recently re-treated. Thirteen of the patients died from complicating diseases during the observation period.

The series included 11 cases in which the thyroid was recorded as only slightly enlarged (probably less than 50 g); 35 with moderately enlarged thyroids (50—100 g); 32 with large goiters (100—200 g), and 8 with very large goiters certainly weighing more than 200 g. The average number of treatments and the average activities used are shown in the following table.

Size of goiter	<i>Small</i>	<i>Moderate</i>	<i>Large</i>	<i>Very large</i>
Number of cases	11 (8)	35 (26)	32 (25)	8 (6)
Still hyperthyroid or recently re-treated	0	3	1	0
Average number of treatments	1.27 (1.37)	1.83 (1.65)	2.22 (2.28)	1.75 (1.67)
Remissions after a single treatment	82 %	49 %	28 %	37 %
Average initial activity in mC	6.4 (5.9)	8.3 (8.8)	13.9 (14.2)	47.5 (59.2)
Average total activity in mC	8.7 (9.1)	13.6 (13.8)	34.3 (35.0)	83.1 (99.2)

(The figures in parentheses refer only to patients who were alive and euthyroid at the end of the observation period.)

Of the four patients who became hypothyroid two had moderate goiters and had received 7+8 mC and 8+8+7+3 mC respectively; two had large goiters (100—150 g) and had received 15+15 mC and 15+25+50 mC respectively. Three of them had severe cardiac complications and the hypothyroidism was a desired (if not expected) result.

The impression gained in this group was that a remission could be obtained quite as easily as in the diffuse toxic goiter cases, provided sufficiently high activities were used and the treatment was repeated as long as the uptake of I^{131} in the thyroid was still high. Even when remission occurs after a single treatment, it has been observed that it takes longer in nodular than in diffuse toxic goiters. In two series a mean value of about 5 months for nodular and about 3 months for diffuse goiters was observed (*Crile et al.* 70, *Moe et al.* 212). In the present series this course was especially pronounced in cases with large goiters, in which a progressive improvement often went on for several months after the treatment, and, moreover, continued diminution of the goiter for half a year or more was sometimes observed (Fig. 30).

Some investigators have found that many toxic nodular goiters have such a low uptake of radioiodine that adequate treatment is difficult or impossible (*Seed and Jaffé, 296*). This observation could not be verified in the present series; all cases examined during the relevant period had an uptake high enough for adequate radioiodine treatment. It was, however, observed that after radioiodine treatment the uptake might be greatly depressed for a very long period, notwithstanding persistent hyperthyroidism or without the appearance of hypothyroid symptoms (Fig. 31). A probable explanation may be that the hormone storage in these glands is so large that the gland can continue to deliver hormone in excess, even though the uptake of fresh iodine for hormone synthesis is inhibited. This observation was most often made in patients with very large goiters; and if the above explanation is correct, it is a further reason why surgery must be superior in these cases. In the observed patients of this type, remission usually occurred slowly or the uptake of radioiodine later increased, so that further treatment was possible.

The goiters diminished considerably in size after the treatment, but in most cases more or less pronounced remnants could be palpated. In only 6 cases was there clinically complete resolution with regard to the palpatory findings. Two of these cases had long-standing exophthalmic goiters, with symmetrically enlarged glands having a nodular, or lobulated, character (Fig. 13). In 30 cases the goiter so diminished that only small remnants of it could be palpated. In the large multinodular goiters there was usually considerable regression, though rather large remnants persisted (Figs. 28 and 30). One patient had a large "solitary" adenoma, and examination by the tracer test revealed little or no uptake in the adenoma but a high uptake in the other parts of the gland. The adenoma, as was to be expected, did not diminish in size after the treatment, despite remission of hyperthyroidism (Fig. 29). Two cases had "solitary" adenomas in otherwise non-palpable glands, and examination by directional counter revealed that the uptake of radioiodine was confined to the palpable adenomas. It is probable that these two cases represented solitary toxic adenomas (*cf. Cope, Rawson, McArthur 67*). Both patients had refused operation — which of course is preferable in these cases — and were treated with radioiodine. In both cases a remission of the hyperthyroidism was obtained, but the adenomas diminished only slightly in size. Examination by directional counter was also done in many cases with multinodular goiters, and usually revealed that the uptake was irregularly distributed over a rather large volume. In the very large goiters, in which it was planned to give extremely high activities,

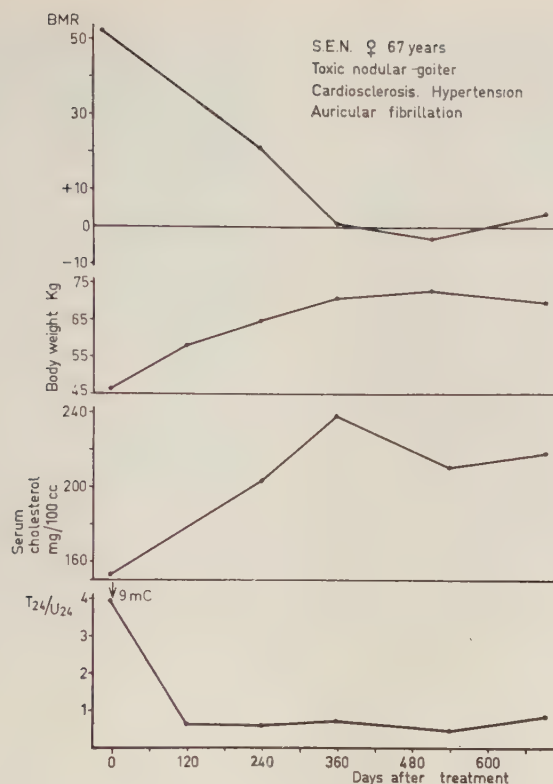


Fig. 27. SEN. R. 3745/52. Woman, 67, with nodular goiter of 30 years standing. Thyrotoxic symptoms since late in 1951, and weight loss of 27 Kg in five months. Heart trouble and auricular fibrillation. B.M.R. +63, +132, +52. She had a moderately enlarged nodular goiter, and a tracer test on May 28, 1952 revealed T_{24} 71 per cent and U_{24} 18 per cent. After a single treatment with 9 mC I^{131} on May 30, 1952, there was a gradual improvement, and she has been euthyroid since about 4—5 months after the treatment. The goiter diminished slowly in size during the first half year after the treatment, and since that time only small remnants persist. She has cardiosclerosis, arterial hypertension and permanent auricular fibrillation, but the subjective heart distress has greatly improved.

such examinations were made routinely. The very high activities were administered only if the isotope was distributed over a large volume.

Some examples of radioiodine treated toxic nodular goiters are given in Figs. 27—31. Fig. 27 shows a patient with a moderately large goiter, hyperthyroidism, cardiosclerosis and auricular fibrillation. She improved gradually after a single treatment and has been euthyroid since about 4—5 months after the treatment. The patient in Fig. 28 had a very large toxic goiter which

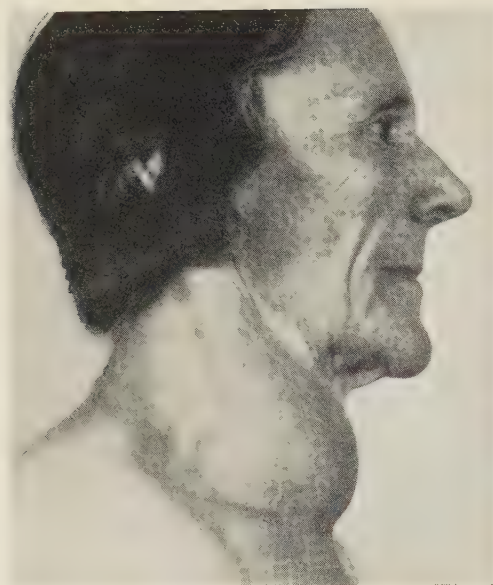


Fig. 28 a.

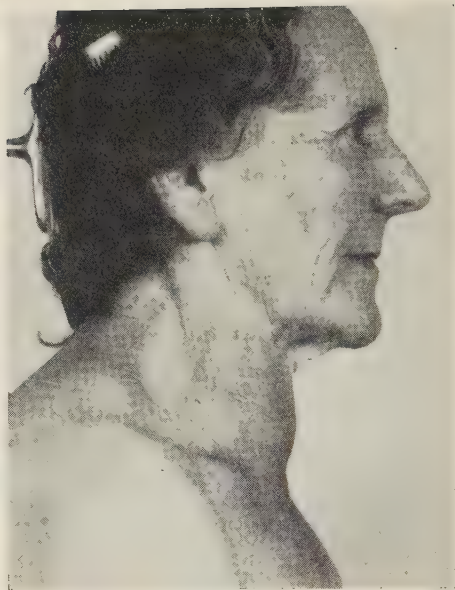


Fig. 28 b.

Figs. 28 a and b. *KVE*. R. 2379/53. Woman, 70, with large nodular toxic goiter; B.M.R. +85; auricular fibrillation and cardiac decompensation. She was treated with 20 mC on April 24, 1953; 50 mC on Sept. 3, 1953; and 20 mC on March 13, 1954. Since the treatments there has been a progressive general improvement and continued decrease of the goiter. A. Before treatment. B. March 11, 1954.

gradually diminished in size after multiple treatments with high activities, concurrently with a remission of hyperthyroidism. Fig. 30 relates to a patient with an extremely large toxic goiter associated with severe pressure symptoms and heart disorder. Some days after treatment with 100 mC, she had a transient exacerbation with increased cardiac decompensation, but has since gradually improved. The pressure symptoms disappeared rapidly and the goiter continued to diminish in size throughout the year after treatment. Fig. 31 shows a woman with a large intrathoracic toxic goiter who had a remission after two treatments; the goiter decreased roentgenologically to about half its original volume. This patient had, for a long period after the last treatment, a very low uptake of I^{131} in the thyroid, but at no time presented clinical signs of hypothyroidism.

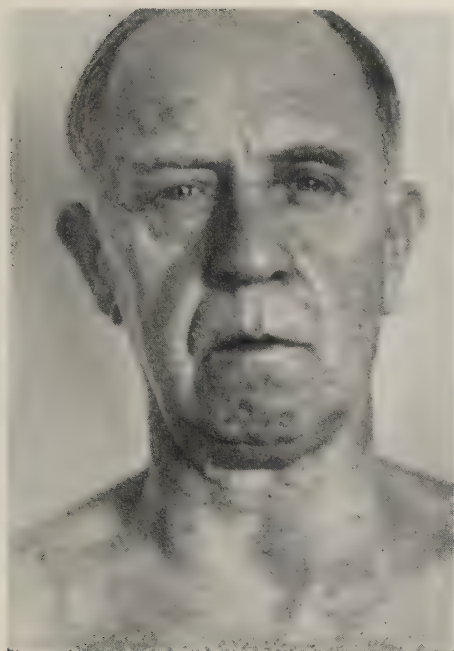


Fig. 29 a.

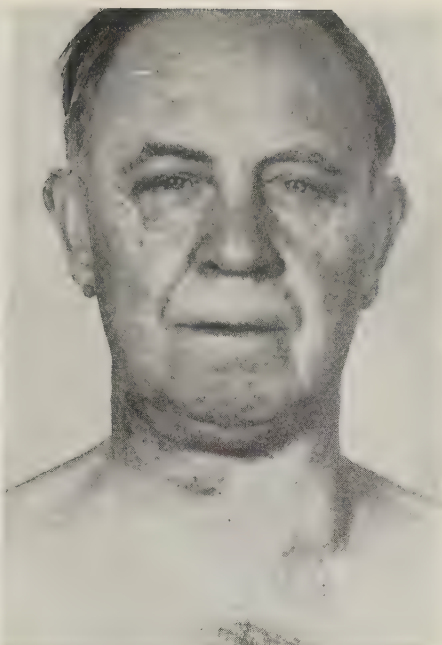


Fig. 29 b.

Figs. 29 a and b. *JHR.* R. 6791/52. Man, 65, with cardiosclerosis and arterial hypertension; recently treated for coronary thrombosis. For several years, observed a growing nodule in the left thyroid lobe. In the last few months, increasing thyrotoxic symptoms, weight loss, nervousness, etc. B.M.R. +45, +50. He had a definite picture of hyperthyroidism. In the left thyroid lobe was an adenoma measuring 5 by 5 cm. Despite the type of goiter he was sent for radioiodine treatment because of the severe cardiac disease. Tracer test on Oct. 9, 1952 showed $T_{24}=62$ per cent and $U_{24}=22$ per cent. Examination by directional counter revealed little or no uptake in the adenoma but a high uptake in other parts of the gland. After 8 mC I^{131} on Oct. 23, 1952, he had a transient exacerbation during the first few weeks, with increasing heart symptoms, but then improved rapidly and showed a distinct remission. The adenoma in the left lobe was, as could be expected, unchanged in size, and further examination by directional counter after a tracer dose, in Feb. 1954, still revealed little or no uptake in the adenoma. He is now clinically euthyroid but still has heart distress from cardiosclerosis and hypertension. SPI in Sept. 1954, 4.8 gamma. The last tracer test on Jan. 19, 1955 revealed T_{24} 33 per cent and U_{24} 50 per cent. A. Before treatment. B. Aug. 31, 1954.

6. Disadvantages and Complications of Treatment

Failure of Remission or Slow Response. — Probably there are extremely few toxic goiters in which radioiodine treatment, once started, cannot bring about a remission or even — at all events in the diffuse goiters — permanent hypothyroidism. All reported series, regardless of the treatment technique used,

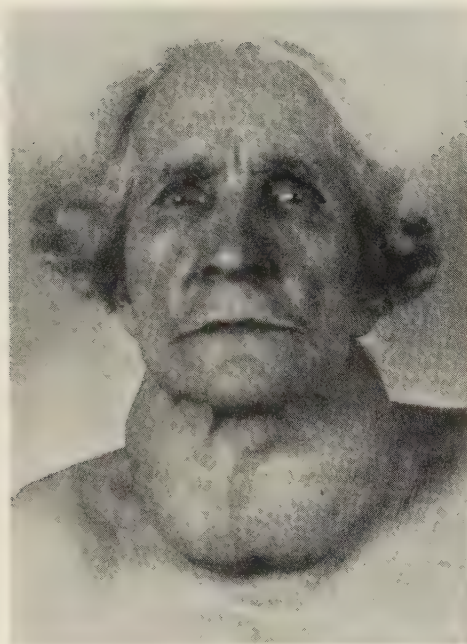


Fig. 30 a.

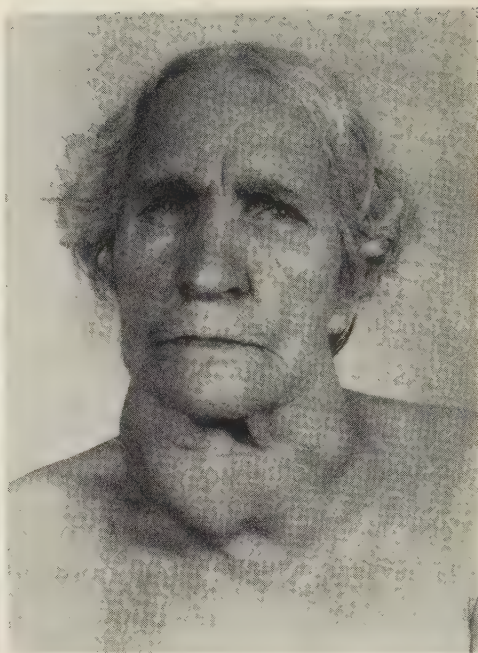


Fig. 30 b.

Figs. 30 a, b and c. *HST*. R. 5866/53. Woman, 75, with large goiter of 15 years' standing. In the last months, increasing pressure symptoms and able to swallow only liquid food. Had also increasing hyperthyroid symptoms with weight loss, nervousness, sweats, intermittent auricular fibrillation and cardiac decompensation. Tracer test on Sept. 23, 1953: T_{24} 63 per cent, U_{24} 4 per cent. She received 10 mC I^{131} on Sept. 25. Since localization measurement showed that the uptake was distributed over a very large volume, this activity seemed inadequate and she received, on Oct. 12, 1953, 100 mC I^{131} . After a transient exacerbation for one week she has gradually improved. The pressure symptoms disappeared during the first few weeks, and the goiter has since continued to decrease throughout the observation period. The thyrotoxic signs have gradually subsided, and she is clinically euthyroid. The attacks of auricular fibrillation have ceased. A. Before radioiodine treatment. B. Feb. 3, 1955.

nevertheless include some cases that have required multiple treatments to produce a remission. In the present series 14 patients were recorded as still thyrotoxic or recently re-treated at the end of the observation period. Four of them had received only one or two treatments and were greatly improved, but recent follow-ups had revealed slight persisting hyperthyroidism, so that further treatment was given. The other patients had all received four treatments or more, and were recently re-treated. Two of them actually had remissions at recent follow-ups after the last treatment, and all of them are more or less improved.

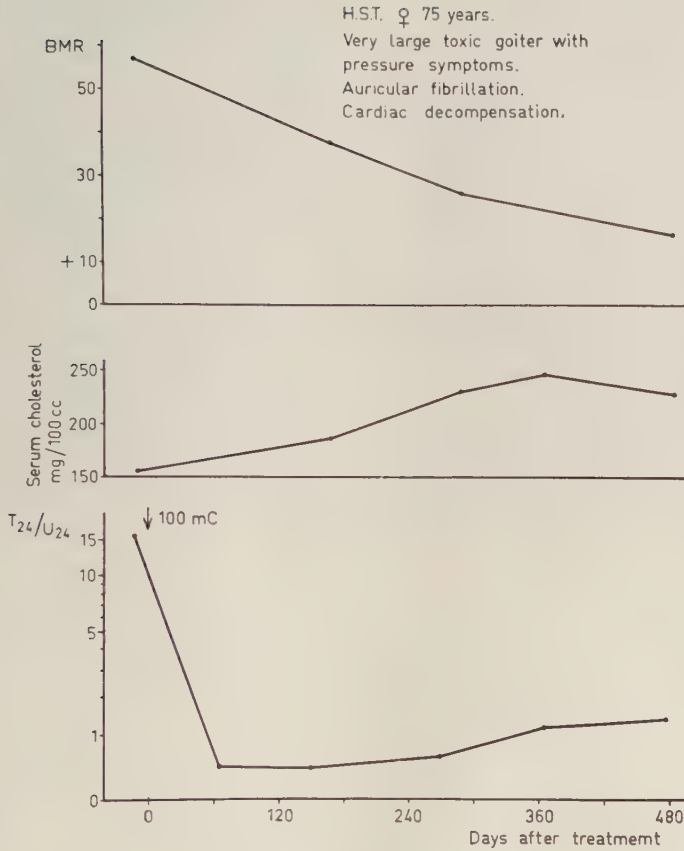


Fig. 30 c.

In this series 61 cases (17 per cent) required more than two treatments and 21 (6 per cent) more than three treatments. Forty-one of 352 living patients (12 per cent) were still hyperthyroid one year after the start of treatment, or were re-treated less than two months before the end of that observation period. Seven of 253 patients (2.8 per cent) were still thyrotoxic or recently re-treated after 18 months, and two of 160 (1.2 per cent) after 2 years. In many of these patients there was a progressive improvement, and the delayed full remission was of little practical importance. In a small group, persisting hyperthyroidism

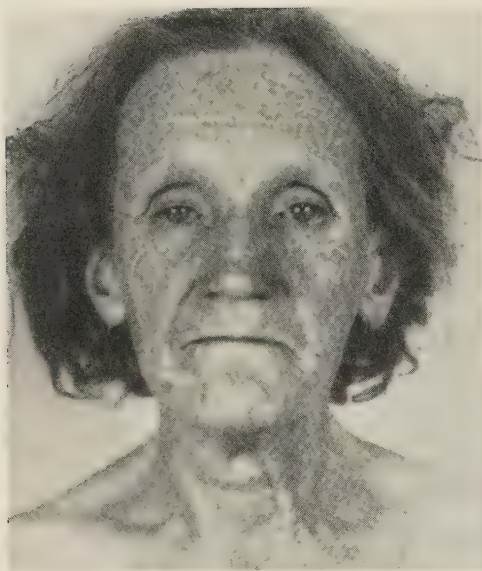


Fig. 31 a.

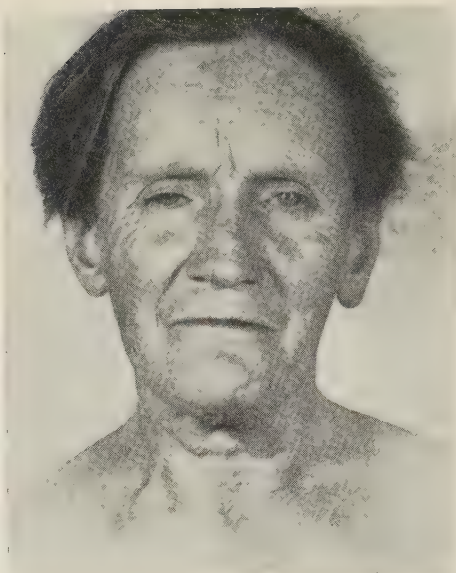


Fig. 31 b.

Figs. 31 a, b and c. *EMH*. R. 1076/53. Woman, 64, with nodular goiter, the bulk of it intrathoracic. Since 1952, increasing hyperthyroidism and heart trouble, with intermittent auricular fibrillation. B.M.R. in Jan. 1953, +75, +60. She had a large, mainly intrathoracic, nodular goiter which, according to the chest roentgenogram, had a volume of about 150 cc. After the first treatment with 30 mC I^{131} she improved but was still hyperthyroid. The next treatment with 50 mC I^{131} produced a further improvement, and she has been clinically euthyroid since some months after this treatment. She has increased in weight from 58.8 to 74.2 Kg. The auricular fibrillation has disappeared and also the subjective heart trouble. The B.M.R. is still somewhat high, but is not consistent with the clinical picture and the other laboratory findings. Despite the marked depression of radioiodine uptake for a very long period after the second treatment, she at no time had signs of hypothyroidism. The intrathoracic goiter has roentgenologically diminished to about half its original volume. A. Before treatment, B. September 1954. C. Laboratory tests.

requiring multiple treatments did cause the patients disappointment and considerably delayed their return to normal life. The series contained 12 patients of this kind, all of whom received four treatments or more. There may be several reasons for these "failures". The average irradiation dose may have been too low, due either to erroneous estimation of the size of the gland or to an unusually short effective half-life of I^{131} in the gland. The latter explanation was highly probable in four of these patients, in whom repeated later examinations revealed very short EHL and high PBI^{131} values after 48 hours. In other cases the explanation may be some biologic variation previously dis-

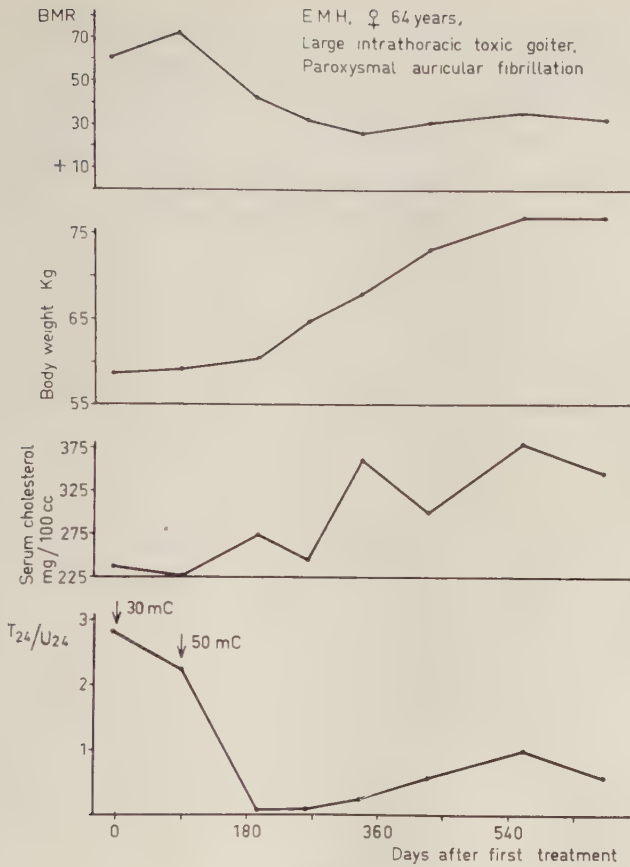


Fig. 31 c.

cussed. In the author's opinion, one of the most urgent problems in radioiodine treatment is to find a method that will reduce the incidence of such cases. *Herner* (362) recommended giving a very high activity in patients who had not responded to the first few treatments. Several cases in this series suggest that this can often be done without producing definite hypothyroidism (see Figs. 20 and 23); and in cases with, for instance, severe heart complications this method is doubtless advisable. *Myant* (cited in 356) routinely used repeated treatment in patients who still had a pathologically increased uptake of I^{131} in the thyroid after a new tracer test three weeks after the treatment. As a rule this seems to be somewhat too early, since the full biological effect of the irradiation cannot be reached after that time. As a means of shortening

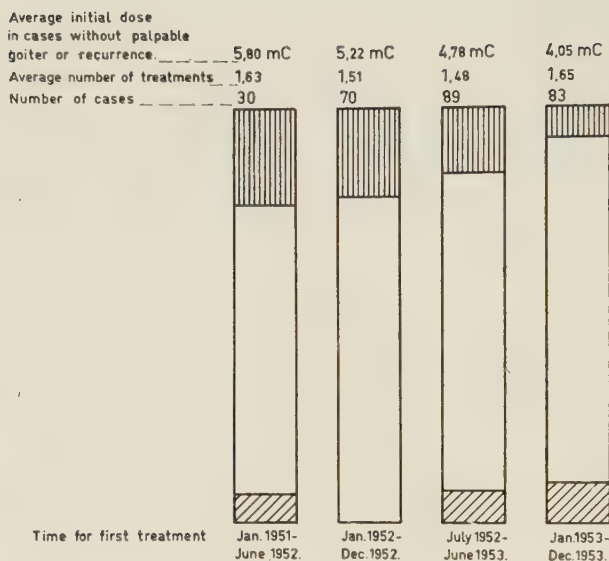


Fig. 32. Comparison of the incidence of hypothyroidism during different periods in patients without demonstrable goiters and those with recurrent diffuse goiters. The columns with vertical lines represent patients hypothyroid one year after the start of treatment; the white columns patients euthyroid at that time; and the columns with oblique lines, patients still toxic after a year or re-treated less than 2 months before that time. The average initial activities given above the columns, refer only to cases with primary or recurrent hypothyroidism in which no goiter was palpable. The other figures refer to the whole group of patients without palpable goiters or with recurrent hypothyroidism after operation. Patients who died within one year as well as the four cases with hypothyroidism induced because of congestive heart failure, are excluded.

the course in patients who have not responded to the first few treatments it seems, however, to be a possibility.

Hypothyroidism. — Transient hypothyroidism is relatively common 2—6 months after the treatment. These cases are more fully discussed in Chapter III in connection with the tracer tests. The figures given in this section with regard to the incidence of hypothyroidism refer only to cases with permanent hypothyroidism. The incidence in the total series and in the different groups of goiters has been discussed in the foregoing. It was rather low among the nodular goiters and the primary diffuse goiters, but considerably higher among the cases without palpable goiters and, especially, those with recurrent hyperthyroidism following subtotal thyroidectomy. These differences (with the ex-

ception of nodular goiters) are probably due, in part at least, to the fact that the small goiters had received, on the average, too high activities in relation to the volume of the gland. With increasing experience of the treatment of these goiters, the incidence of hypothyroidism was gradually reduced. In Fig. 32 the incidence of hypothyroidism one year after the start of treatment is illustrated for different periods in respect of the two groups with the highest incidences, *i.e.*, cases without demonstrable goiter and cases with recurrent hyperthyroidism after operation. (Patients who died within one year and the four cases with "intentional" hypothyroidism are excluded.) The incidence of hypothyroidism decreased gradually from 23 per cent to 7 per cent, with only slight changes in the average number of treatments required. The amounts of the initial activity were compared in the cases without palpable goiters or palpable recurrences. The average initial activity given in these groups decreased, during the periods investigated, from 5.8 mC to 4.0 mC. Even the latter activity seems to be somewhat too high for most of these patients, and they are now usually treated with initial activities of 2—3 mC. *Seed and Fields* (295) wrote of such cases: "One might assume that because there is no palpable goiter a small dose would be sufficient. This has not been our experience. The patient with recurrent symptoms of moderate to severe degree and no palpable gland requires 6—8 mC for effective treatment." In the present investigation quite a different experience was gained.

In the total series too, a considerable decrease in the incidence of hypothyroidism emerges on comparison of an earlier and a later period:

Year of treatment	1951—1952	1953
Number of cases	174	187
Hypothyroidism	33 (19 %)	15 (8 %)
"Unintentional" hypothyroidism	32 (18 %)	12 (6 %)
Hypothyroidism one year after the start of treatment	21 (12 %)	11 (6 %)
"Unintentional" hypothyroidism one year after the start of treatment	21 (12 %)	9 (5 %)
Still hyperthyroid or recently re-treated after one year	18 (10 %)	23 (12 %)
Average number of treatments	1.70	1.74

The incidence of hypothyroidism was thus reduced to about half, with insignificant changes in the average number of treatments required and in the number of patients still hyperthyroid one year after the start of treatment. This difference can only partly be due to the hypothyroidism of late onset,

since the difference in the incidence of hypothyroidism after one year was also pronounced.

In most cases the hypothyroidism already appears during the first 6 months after treatment. It has been observed, however, that hypothyroidism may not appear for a long time, sometimes several years (*Miller et al.* 207, *Seed et al.* 296, *Chapman et al.* 58). Only a few cases of this type were observed in the present series, but some additional cases have slight signs of hypothyroidism, not yet requiring substitution therapy, and it seems probable that the incidence of hypothyroidism in the series will increase somewhat after prolonged observation. The following table shows the intervals between the last treatment and the start of substitution therapy in the cases with permanent hypothyroidism.

Less than 6 months	26 cases
6—12 months	10 „
12—18 „	7 „
18—24 „	3 „
More than 24 months	2 „

The incidence of permanent hypothyroidism varies considerably in different series; figures of from 4 to 25 per cent have been reported in large series, with an average of about 10 per cent. It is difficult to compare these figures, as the composition of the series may have greatly influenced the incidence. With the experience gained in this series it was relatively easy to treat primary diffuse goiters without causing hypothyroidism, in contrast to recurrent goiters. It was previously mentioned that in one of the groups (hyperthyroidism without palpable goiter) the incidence of hyperthyroidism was lower in older subjects. If the patients with nodular goiters, as well as those who died during the observation period and the four with “intentional” hypothyroidism are excluded, the total series will comprise 212 patients under 60 years and 59 patients of 60 years or over. In the former group, 37 (17 per cent) showed hypothyroidism and in the latter group only three (5 per cent).

Initial Reactions after Radioiodine Treatment. — Two types of reactions may occur soon after the treatment and have been recorded in most published series. The first is a local reaction with swelling and tenderness of the thyroid, and more rarely, reactions in the trachea and esophagus. Slight reactions of this type are very common, and were not specially recorded in the present series. No case with any severe local reaction was noted in this series, but the author

has since observed one patient with a large nodular goiter, in whom administration of a high activity was followed, after a few days, by somewhat threatening symptoms, with severe swelling of the goiter and signs of pressure.

The other type of reaction is an exacerbation of the hyperthyroid symptoms, usually during the first two weeks after the treatment. Elevation of SPI has been observed in some cases during the first days after treatment (*Chapman et al.* 54, 198, *Soley et al.* 317), and it has since been demonstrated that this rise is probably due to thyroglobulin released from the thyroid during the cellular destruction (*Robbins et al.* 270). During the same period an elevated sedimentation rate may be observed too (*Soley et al.* 317). In most patients no clinical signs of exacerbation can be noted, but in some there may be more or less severe symptoms, and even fatal crisis has been observed. In patients with severe cardiac complications these exacerbations may involve a special risk. In several patients in the present series a pronounced increase of cardiac decompensation was observed soon after the treatment. In two of the patients it seems likely that an exacerbation after the treatment was a contributory cause of death; these cases will be discussed later. It seems obvious that patients with a low cardiac reserve should always be admitted and not treated as outpatients. The possibility of avoiding exacerbations by specific pre- and post-treatment has previously been discussed. The incidence of really serious exacerbations does not, however, seem to be high enough to indicate more general use of these methods.

Progressive Exophthalmos. — Severe progressive exophthalmos may occur spontaneously and is also a dreaded, though rare, complication after subtotal thyroidectomy. Some cases of progressive exophthalmos have also been described after radioiodine treatment (*Gordon et al.* 108, *Werner et al.* 365, and others). Some authors have stated that the tendency to increasing protrusion is less after radioiodine treatment than after surgery (*Sweeney et al.* 331, *Clark et al.* 62, *Ferguson* 85). *Soley et al.* (317) measured the protrusion in 47 cases with exophthalmic goiter and found no change in 31, a slight increase in 12, and a marked increase in 4 cases. Some authors (*Chapman et al.* 57) have regarded hyperthyroidism associated with pronounced exophthalmos as a special indication for radioiodine treatment, due to the slower depression of the thyroid function that follows the use of that method.

In the present series, 127 cases (54 primary diffuse goiters, 47 recurrent diffuse goiters, 23 cases without demonstrable goiter, and 3 with nodular

goiters) had ocular symptoms in the form of exophthalmos, lid retraction or lid edema. Seven of these cases had shown eye symptoms of malignant type, but they were in a stationary phase when the treatment started. As in surgical treatment, there was usually a cosmetic and subjective improvement of the eye symptoms, with diminished lid retraction and lid edema (Figs. 14, 18 and 21). The behavior of the protrusion was not followed objectively. In 11 cases, however, a definite increase in the eye symptoms occurred after the treatment. One of these cases already had pronounced exophthalmos before the treatment, and it continued to increase after radioiodine treatment. The other patients had only slight or moderate ocular symptoms before the treatment. In these cases a pronounced increase of those symptoms was noted several months, and even years, after the radioiodine treatment; there were marked orbital and lid edema, protrusion and, in five of the patients, ocular muscle weakness with incoordinated eye movements and diplopia. In three cases this exacerbation was concomitant with hypothyroidism; the other patients were euthyroid. No case in this series showed rapidly increasing malignant exophthalmos within the first few months after treatment.

Other Complications. — Blood changes are not infrequently observed after the very high activities given in patients with thyroid carcinomas, but very seldom after activities usually given for hyperthyroidism. A few patients in this series received high activities (50—100 mC), but no significant changes in the peripheral blood cell picture were observed.

One case with hypoparathyroidism following radioactive iodine treatment for thyrotoxicosis has been described (*Tighe*, 346). Lesions of the parathyroids in connection with radioiodine treatment have usually been regarded as unlikely; *Soley et al.* (317) showed that the activities used for hyperthyroidism in man were, in relation to body weight, only about one-fortieth of the activity required for destruction of the parathyroids in mice. It is probable, however, that in rare cases with parathyroids completely enveloped by thyroid tissue the beta-radiation would be sufficient to cause relative hypoparathyroidism. In this series one case was observed which after two radioiodine treatments, had signs suggestive of hypoparathyroidism, and a blood calcium value of 7.9 mg per cent. This patient had, however, previously been subjected to subtotal thyroidectomy, and since the blood calcium was not investigated before radioiodine treatment started, it is impossible to know if this treatment was the cause.

*Prévo*t and *Horst* (246) reported appearance of rheumatoid arthritis in

some radioiodine treated patients. *Bauer* and *Goodwin* (24) noted acne and gynecomastia in some cases. In both cases the authors attributed these findings to some general hormonal disturbance (thyroid-adrenal-pituitary interrelation) and not to a specific effect of radioiodine treatment. No similar observations were made in this series.

Causes of Death. — In the total series 23 patients (6.2 per cent) died during the period of observation. This figure seems relatively high, but is not remarkable in view of the high mean age in the series and the large number of cases with serious complicating diseases.

Two patients died of malignant tumors (gastric carcinoma, hypernephroma), two of bleeding gastric ulcers, one of peritonitis caused by a perforating ulcer in a congenital diverticulum of the intestine (Meckel), and one of diabetic coma.

Seventeen patients died of cardiovascular complications, 13 of them from 3½ months to 1½ years after the last radioiodine treatment. Eight of them were definitely euthyroid after the last treatment. The functional state of the thyroid in the remaining cases could not be evaluated, though it seems most probable that three of them were still thyrotoxic, but due to their poor condition they could not be sent for re-treatment.

In four of the patients who died of cardiovascular diseases, death occurred within 3 months after the last treatment, and in two of them it is likely that an exacerbation after the treatment was a contributory cause of death. One of these patients was a woman with severe syphilitic aortitis, arterial hypertension and chronic pulmonary congestion, previously treated with iodine and propylthiouracil for threatening thyrotoxic crisis:

GVS. R. 973/53 Woman, 50, with hypertension of several years standing and, since Aug. 1952, increasing heart distress, tachycardia, nocturnal attacks of dyspnea, and also increasing signs of hyperthyroidism. Admitted to a medical department on Sept. 29, 1952. Diagnosis: Syphilitic aortitis, aortic insufficiency, cardiac decompensation with chronic pulmonary congestion.

Heart volume 1,700 ml. Intermittent auricular fibrillation. Severe hyperthyroidism with high pulse rate and B.M.R. + 50- + 60. Moderate goiter with a nodular part in the left lobe. No ocular symptoms. She was treated with iodine and propylthiouracil; improved and was able to continue on thiouracil alone. She still had a high B.M.R., about + 50, and a high pulse rate, wherefore radioiodine treatment was recommended. Thiouracil was discontinued on Feb. 11, 1953. Tracer test the same day revealed $T_{24} = 52$ per cent and $U_{24} = 26$ per cent. A new tracer test on Feb. 25 revealed $T_{24} = 51$ per cent and $U_{24} = 31$ per cent. She now had rather severe signs of hyperthyroidism with a very high pulse rate, and received on March 12, 1953, 6 mC I^{131} . After about 2 weeks her condition progressively deteriorated and, on April 15, she was admitted to the same department with

increased cardiac decompensation and signs of severe hyperthyroidism. She was treated with iodine and propylthiouracil with a transient improvement, but deteriorated again and died on April 15 after a period of increasing pulse rate, fever and cardiac decompensation. Autopsy revealed pronounced syphilitic aortitis.

The other patient was a 69-year-old woman with a nodular toxic goiter, cardiosclerosis, auricular fibrillation and cardiac decompensation:

AEA. R. 8543/53 Woman, 69, with goiter since her youth. Heart trouble of several years standing, due to cardiosclerosis and arterial hypertension. Increasing heart symptoms since the spring of 1953. Increasing signs of hyperthyroidism since the same time. Auricular fibrillation. BMR +48, +45. Roentgen treatment to the thyroid in Oct. 1953, without improvement. She was sent for radioiodine treatment in Dec. 1953, and a tracer test on Dec. 21 revealed $T_{24} = 54$ per cent and $U_{24} = 12$ per cent. She had a large nodular goiter (about 150 grams) and a definite picture of hyperthyroidism. On Dec. 29 she received 12 mC I^{131} . She was sent home on Dec. 31 for continued ambulatory control. From Jan. 3 her condition deteriorated, with increasing signs of cardiac decompensation, and on Jan. 6 she was admitted to a hospital in a rather poor condition, with severe dyspnea and tachycardia. She died on Jan. 11 after increasing circulatory insufficiency.

The rule followed for patients referred from provincial hospitals was, otherwise, either to arrange for them to be sent back immediately for continued control at the referring hospital, or to keep them until the most critical time had been passed. This case was an unfortunate exception from this rule, and it further demonstrates the importance of careful control of complicated cases the first few weeks after the treatment.

CHAPTER III

Behaviour of the Tracer Tests after the Treatment

1. General Considerations

There is no reason to believe that the biologic action of I^{131} differs from other types of ionizing radiation; the only difference probably lies in the distribution of the dose in space and time.

The spatial distribution of the dose is always irregular, but far more so in nodular than in diffuse goiters. Radioiodine is a highly selective form of irradiation treatment, partly due to the specific uptake in the thyroid tissue and partly because *beta* particles with a short range in tissue are responsible for the main part of the biologic action. For these two reasons enormously high irradiation doses may be delivered to the thyroid tissue without serious damage to the surrounding tissues or to other parts of the body.

Treatment with I^{131} (8 days half-life) is a protracted radiation treatment. Due to the accumulation of I^{131} and its biologic and physical decay in the gland, the dose rate is gradually changing throughout the treatment, with a maximum usually occurring within the first day or two after the intake. The effective half-life of I^{131} in a toxic goiter may vary from one to eight days but in most cases is from 2 to 7 days (*Miller et al.* 209; *Freedberg et al.* 91—93; *Blomfield et al.* 36; *Horst et al.* 151, 153, 155). If the EHL is 2 days, about 90 per cent of the irradiation dose is delivered within the first week, but if it is 7 days it will take a little more than three weeks for the same portion of the dose to be delivered. The distribution of the dose in time thus varies widely in different patients. As in all forms of radiation treatment, a latent period must be expected between irradiation and maximal biologic response. The length of this period is usually dependent upon the size of the dose, the time factor and the radiosensitivity of the treated tissue. It can scarcely be studied, however, after I^{131} treatment, due to the protracted character of the therapy.

The histologic effects of internal irradiation with I^{131} have been studied both in experimental animals and in euthyroid and hyperthyroid human beings (*Gorbman*, 106; *Goldberg et al.* 103; *Dailey et al.* 73, 186; *Maloof et al.* 199, 77; *Freedberg et al.* 95). The changes observed accord with those usually

described in connection with irradiation treatment, *i.e.*, cytologic changes with chromatin disturbances, inflammatory stroma reactions and, as late sequelae of the irradiation, fibrosis and atrophy. Two findings are of special interest in connection with the functional behaviour of the gland after the treatment. Both in animals and in man there have been observed, after sufficient time, signs of regeneration (*Goldberg et al.* 103; *Lindsay et al.* 186). Histologic pictures indicating that the remnant of the gland is influenced by an excessive extrathyroid stimulation (TSH) have also been reported (*Maloof et al.* 199; *Lindsay et al.* 186).

In an endocrine organ the functional changes are of greater interest than the morphologic ones. The thyroid gland is not an autonomous organ; functionally it is highly dependent upon the interrelation with other endocrine organs, especially the pituitary gland. When the thyroid function is studied after any type of therapy, the observed changes must be regarded as the net result of the changes in the thyroid and of those in its pituitary stimulation provoked by the altered level of circulating thyroid hormone. The interrelation between the pituitary and the thyroid in cases with exophthalmic goiter is still a much discussed topic. That the "feed-back" mechanism between the thyroid and the pituitary exists in cases with remissions after surgical or radiologic treatment has, however, been clearly demonstrated (*Werner et al.* 367, 371; *Horst* 153, 155; *Morgans et al.* 213).

In an experimental series the thyroid function may be studied in many ways after I^{131} treatment. The iodine content of the gland, the ability of the gland to enlarge after treatment with TSH or thiouracil or after iodine-deficient diet, its capacity to accumulate radioiodine, and the level of SPI, have thus been studied and have proved to be sensitive indices of an irradiation effect (*Skanse* 305, 306, 309; *Maloof et al.* 199; *Feller et al.* 84). *Goldberg et al.* (102) studied, in rats the cytologic changes produced in the anterior pituitary by the diminished level of circulating thyroid hormone after I^{131} treatment. Of major interest was their finding that after some dose levels the changes indicated a severely depressed thyroid function during the first few months, followed by recovery or regeneration after about 5—8 months.

As regards the very early changes after the treatment, the fate of the therapeutic dose itself has yielded valuable information. It has thus been observed, both in animals and in man, that after sufficiently high amounts of I^{131} the thyroid collection curve differs from that after a small tracer dose (*Skanse* 305, 306, 309; *Gorbman* 106; *Maloof et al.* 199; *Robbins et al.* 270).

The initial rate of uptake is usually the same, but after some time I^{131} disappears more rapidly from the gland after the therapeutic dose than after the tracer dose, indicating a biologic effect of the irradiation. This is probably attributable to the release of labelled thyroglobulin from the gland during the cellular destruction, as has been demonstrated by an analysis of the different I^{131} fractions in the blood after the therapeutic dose (*Tong et al.* 347; *Robbins et al.* 270; *Stanbury et al.* 320). Other manifestations of the same mechanism are probably the early rise in the SPI values sometimes observed after the treatment (*Riggs* 267; *Maloof et al.* 198) and also the increase of the sedimentation rate (*Soley et al.* 317).

Many of the last-named observations have been made after very large doses; in man often after the large doses given for complete ablation of the thyroid tissue in patients with cardiac failure or patients with metastasizing thyroid carcinoma. A similar effect certainly occurs also after I^{131} treatment of hyperthyroidism, but probably it is not a mechanism of any major importance or one essential for a sufficient therapeutic effect. Rather it must be assumed that the depression of the thyroid function in most cases occurs gradually during the first few weeks or months after the treatment.

In practice the most important indicators of the thyroid function after treatment are the clinical picture and the conventional laboratory tests, *i.e.*, BMR, SPI, uptake of I^{131} , and serum cholesterol. These tests have different positions in the chain of events: the accumulation of I^{131} reflects the ability of the gland to utilize iodine for hormone synthesis, SPI reflects the level of circulating thyroid hormone, and BMR and serum cholesterol are, like the clinical picture, criteria of the peripheral action of the thyroid hormone. During the initial phase after treatment, when the functional changes in the thyroid proceed rather rapidly, the different tests cannot be expected to keep pace with each other. It is of some interest to compare the events after total surgical thyroidectomy. The uptake of I^{131} will be zero immediately after the operation, as all thyroid tissue is removed. The SPI will not change at once, but after a time will fairly rapidly reach myxedema values when the circulating thyroid hormone is utilized. The serum cholesterol and BMR, which both reflect the peripheral action of the hormone, change more slowly, and only after some considerable time will the clinical picture reveal all the features of myxedema.

After subtotal destruction of the gland with I^{131} the events will be more complicated for several reasons. Due to the protracted nature of the treatment

and to the latent period between irradiation and full biologic response, the functional changes occur gradually. Since the destruction is not complete, the events are also complicated by regenerative phenomena, recovery of temporarily inhibited cells or of a compensatorily increased function in surviving tissue.

It would be of great interest to study the correlation between the different laboratory tests and the clinical picture after I^{131} treatment. As regards the tracer tests, BMR and serum cholesterol, one part of the series would have been suitable for such a study. During this work, however, it was found to be a subject extensive enough to warrant analysis of the behaviour of the tracer tests after treatment and the correlation between these and the clinical results. The tracer tests have several sources of error, both technical and "physiological", and far-reaching conclusions can never be drawn from single observations. A high uptake of I^{131} may be due to iodine deficiency and a low uptake to unknown iodine intake in excess. Incomplete collection of the urine may cause substantial errors, and anatomical variations may make the uptake measurements less reliable. Renal failure and cardiac decompensation may influence the behaviour of the tracer dose. Nevertheless, the impression gained in this series was that the tracer tests usually afforded very useful information, provided that the sources of error and the limitations of the tests were realized. From the practical point of view it is of great importance to know if these simple tests can be used not only as routine pre-treatment measures but also as a diagnostic guide for management of the patient after the therapy.

2. The Accumulation of I^{131} in the Thyroid

The early literature contains remarkably little information on this subject. *Soley et al.* (317) studied in 15 patients the uptake of I^{131} before and after the treatment and found average values of 61 per cent and 16.6 per cent respectively. They also noted three patients with clinical signs of hypothyroidism despite a normal or high uptake. *Freedberg et al.* (93) found that 17 euthyroid patients, who had been treated for hyperthyroidism with I^{131} five to 39 months earlier, had an average 24-hour uptake of 38 per cent, compared with an average of 69 per cent in 48 untreated hyperthyroid patients. The uptake was, however, somewhat higher in patients euthyroid after radioiodine treatment than in normal subjects, the 32 of whom showed a mean of 29 per cent. *Ansell et al.* (9) studied the 4-hour uptake and the

thyroid clearance in 8 subjects and found that these tests were normalized after successful treatment. That the accumulation of I^{131} in the thyroid was usually normalized after the treatment was also observed by *Horst* (151).

In the above-mentioned reports no special regard was taken to the time relations after the treatment. When this study was started it was planned to repeat the tracer tests at regular intervals after the treatment, in order to observe the variations in the I^{131} accumulating ability of the gland. It soon became evident that the uptake of I^{131} in the thyroid was often depressed after about 2—3 months but increased again after a further 2—3 months. The first two systematic studies of this early response to I^{131} treatment appeared almost simultaneously, but had been conducted independently (*Myant* 218; *Larsson and Ragnhult* 180). *Myant* used as a tracer test the neck-thigh ratio 2 hours after the administration (a test which gives values roughly proportional to the thyroid clearance). He made his investigations after three weeks, following a total of 36 treatments. In eight cases the accumulation of I^{131} was more or less unchanged, and these were still thyrotoxic when followed up several months later. In 28 cases the I^{131} accumulating power of the gland was markedly depressed after 3 weeks, and 20 of these cases had definite remissions. In many of the cases with a low uptake after 3 weeks, the uptake had returned to a normal level a few months later, and sometimes even to an abnormally high level despite clinical euthyroidism.

In the other report (*Larsson and Ragnhult*, 180), the 24-hour uptake was used as a tracer test and the series contained 23 hyperthyroid subjects and 10 euthyroid cardiac patients, all treated with I^{131} . The first test was usually done 6—12 weeks after the treatment and the next one after a further 2—3 months. Many patients had a considerable depression of the uptake at the time of the first tracer test but showed recovery of function at the later tracer test. It was also observed that in a minor proportion of the patients with very low uptakes after 6—12 weeks, progressive clinical signs of hypothyroidism later developed. The euthyroid cardiac patients were treated with smaller doses (6—8 mC) than had normally been used in this condition (*Blumgart et al.* 38, 39, 89); and in this group too, there was often a transient depression of the iodine-concentrating function, followed by recovery. Treatment with such small doses is probably not ideal, due to the difficulty of producing an adequate degree of permanent hypothyroidism. Nevertheless, it was of interest to know that this initial transient effect on the accumulation of I^{131} in the thyroid was similar in hyperthyroid and euthyroid subjects.

In each of the above-mentioned papers attention was drawn to the major value of early tracer tests for the practical management of hyperthyroid subjects, and also to the prognostic value of those tests.

Horst (153, 155) found that after transient depression of the I^{131} accumulation, that function once more reached an abnormally high level in some cases, despite permanent remission. This observation was most evident in the 2-hour uptake, but as regards the 24-hour uptake it was often masked due to rapid release of organic I^{131} from the thyroid.

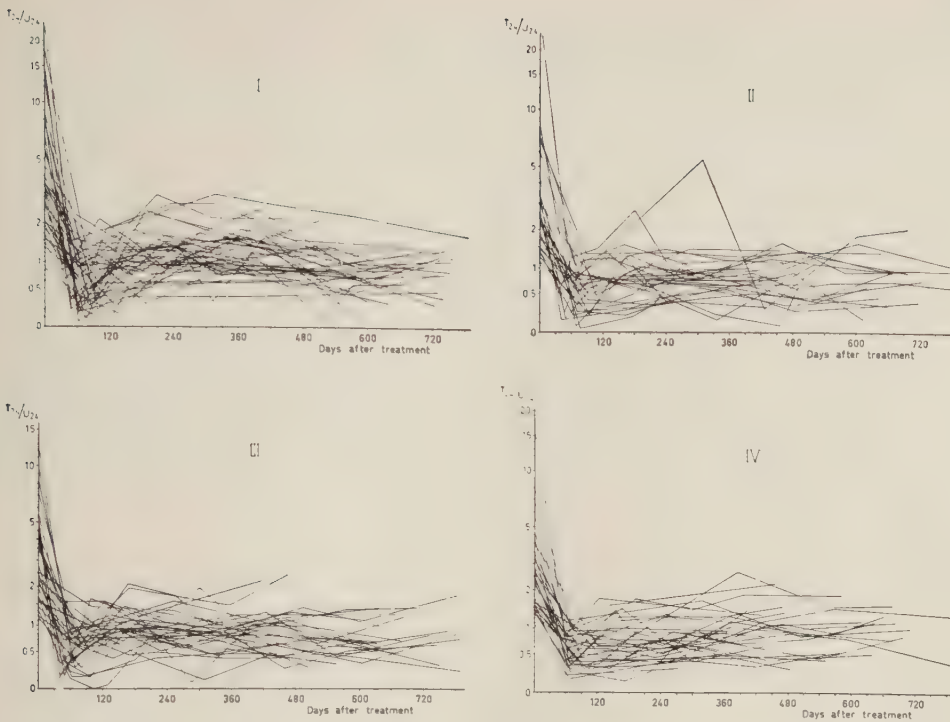
In the following the results of further observations made during the last few years are reported. The cases are classified according to the clinical end result after a single treatment; *i.e.*, patients with permanent euthyroidism, patients with permanent hypothyroidism, and, lastly, failures.

Cases Euthyroid after the Treatment. — The results of the tracer tests (T_{24}/U_{24}) in 125 cases that were euthyroid one year after a single treatment and had undergone repeated tracer tests are illustrated in Figs. 33—36. The cases are grouped in the same way as before, *i.e.*, primary diffuse toxic goiters, recurrent diffuse toxic goiters, primary hyperthyroidism without demonstrable goiters, and toxic nodular goiters.

A few cases, in which the treatment was given even though the preceding tracer test was still influenced by previous iodine medication, have been excluded, as has a further case in which the uptake before treatment was low without any known excessive iodine intake. If a patient had an excessive iodine intake after the treatment (for instance, gallbladder roentgen examination), all subsequent tracer tests were excluded. In patients who had received thiouracil, this treatment was usually discontinued at least one month before the radioiodine treatment, but in a minor proportion of the cases it was continued up to a few days before the preceding tracer test. All these cases had tracer tests of "hyperthyroid type" before treatment. It is possible that thiouracil may change the radiosensitivity. If the patients, however, were grouped according to the end results, the average behaviour of the tracer tests did not differ from that in the other patients. These cases have therefore been included and not reported separately. A few patients received substitution therapy of short duration for transient hypothyroidism; in these cases all tests carried out during the substitution therapy or within two months after its withdrawal were excluded.

The foregoing is valid for all the data presented in the following. No subjective exclusion of data occurred and, with the stated exceptions, only tests that were influenced by known technical errors or by known incomplete collection of urine were omitted.

As shown in Figs. 33—36, there was a fairly wide distribution of the values, though this was to be expected and was also observed in the previously



Figs. 33—36. The changes in the tracer tests (T_{24}/U_{24}) in 125 patients euthyroid after a single treatment. I. Primary diffuse goiter. II. Recurrent diffuse goiter. III. Primary hyperthyroidism without demonstrable goiter. IV. Nodular goiter.

reported euthyroid control series. These composite curves show clearly that in many cases there was a pronounced depression of the uptake during the first few months after treatment, usually followed by a more or less rapid "recovery" of the function during the ensuing months. The course was fairly uniform in the different groups. The pronounced initial depression of the uptake was, however, not quite as common in the toxic nodular goiters as in the diffuse goiters, and when it occurred the recovery often proceeded more slowly. This initial depression of the iodine-collecting ability of the gland is exemplified by several cases in Chapter II (Figs. 17 c, 18 c, 21 c, 25), and also the rather slow "regeneration" sometimes observed in toxic nodular goiters (Figs. 30 c, 31 c).

In Fig. 37, average curves for T_{24} and U_{24} in the same 125 cases are illustrated, and in Fig. 38 corresponding average curves for the tracer tests after the last treatment in 124 patients who did not become euthyroid until

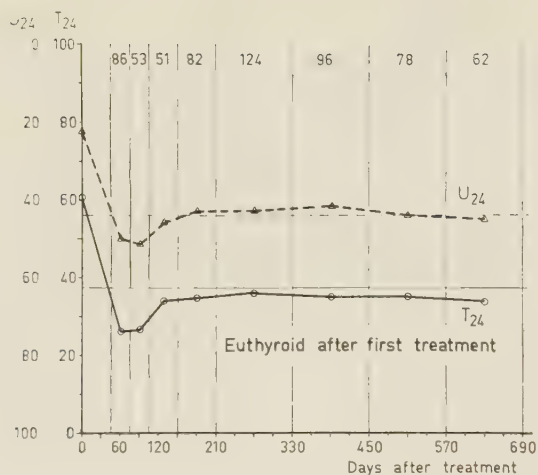


Fig. 37. Average T_{24} and U_{24} values for different intervals in 125 patients euthyroid after a single treatment. The figures above the curves denote the number of observations in each interval.

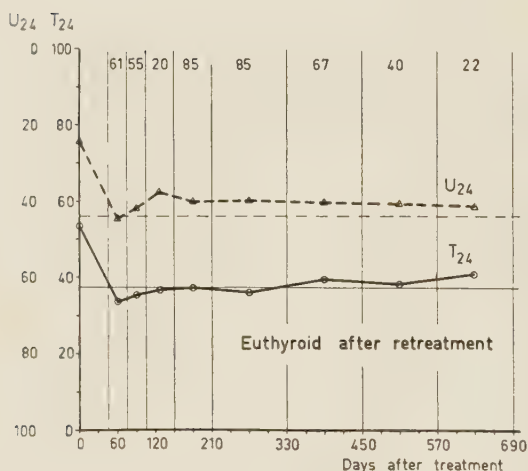


Fig. 38. Average values for T_{24} and U_{24} in 124 patients euthyroid after re-treatment.

repeated treatment had been given. In the first-named curves the depression of the function after about 2 and 3 months is clearly demonstrated; the average value for T_{24} after about 2 months (46—75 days) was 26.2 per cent and after about 3 months (76—105 days) 26.7 per cent. The average values had returned to a fairly stable level after about 6 months, and those for T_{24} varied, in respect of this and the subsequent periods, from 33.9 to 36.2 per cent and were thus close to the average value in the euthyroid controls. The average values for U_{24} were closely consistent with those for T_{24} .

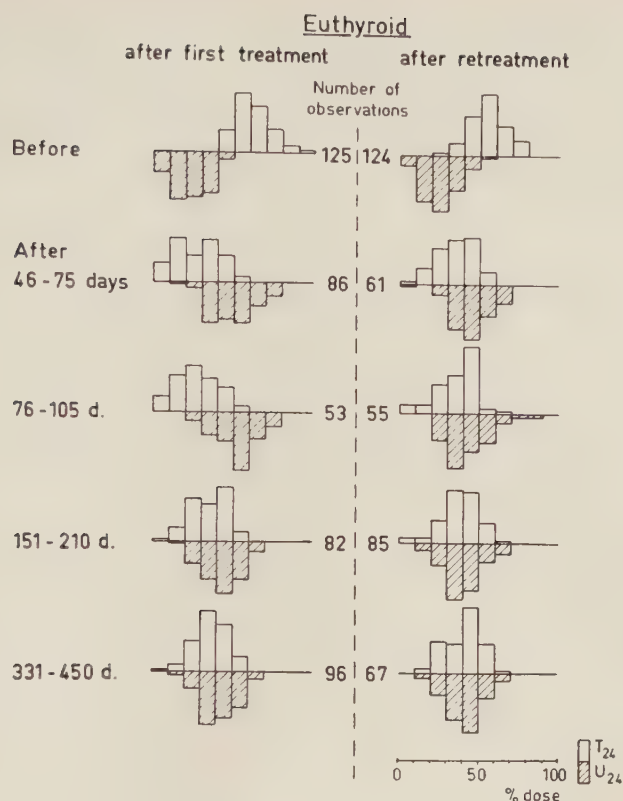


Fig. 39. Distribution diagrams of T_{24} and U_{24} for different intervals in patients euthyroid after the first treatment and patients euthyroid after re-treatment.

As will be seen from Fig. 38, the behaviour of the tracer tests conspicuously differed in the patients who were only euthyroid after re-treatment. In the average values the early depression of the uptake below the mean level was very little pronounced. The difference is even more obvious when the distribution diagrams in Fig. 39 are studied. After 2 or 3 months the uptake was seldom depressed to the low level often found after the first treatment. As from three months the distribution of the tracer tests was fairly similar for the different intervals, in striking contrast to the state of affairs after the first treatment. This difference has not previously been reported, and all explanations will have to be hypothetical. It is probable that when the gland is destroyed step by step, as in multiple treatments, lesser depression of the function will be required for permanent remission. The impression was also gained from this series that when the uptake was greatly depressed after

re-treatment, there was a greater risk of permanent hypothyroidism than when the same phenomenon was observed after the first treatment. It seems likely, and is consistent with both these observations, that the gland has a lesser reserve capacity for recovery after repeated treatment than after the first treatment.

After 6—10 weeks there was often a pronounced discrepancy between the clinical picture and the result of the tracer test. Persistent clinical hyperthyroidism was often noted despite a normal or subnormal uptake, and some cases had an extremely low uptake without presenting clinical signs of hypothyroidism. Some, though far from all, cases with a very low uptake after about 2 months, later showed signs of transient hypothyroidism. If only patients with definite clinical signs of hypothyroidism are included, the series contains 23 cases of this kind. In 15 of these cases the transient hypothyroidism appeared after the first treatment; in 12 of these the uptake was considerably depressed after 2—3 months, with T_{24} values of 3 to 16 per cent. In two of the patients normal or supernormal uptakes were noted despite clinical hypothyroidism; the remaining case was not examined with tracer tests during this period. Eight cases had pronounced transient hypothyroidism after repeated treatment. In four of them the uptake was depressed to 2—17 per cent, while the other four had minimum values from 20 to 46 per cent after 2—3 months.

That the clinical picture did not keep pace with the changes in the tracer test was often especially evident in these cases, and sometimes a rather paradoxical discrepancy was observed. Some cases thus had a very low uptake after about 2 months, yet presented no signs of hypothyroidism. When they were re-examined after a further 2 months, clinical signs of hypothyroidism had appeared but the uptake had returned to a normal level. A typical example of this kind is illustrated in Fig. 17 c, Chapter II. Several of the patients with pronounced transient hypothyroidism were, however, characterized by an unusually slow recovery of the thyroid function, as illustrated by the following example.

I.T.K.E. R. 2636/52. Woman, 67, operated on in 1937 for diffuse toxic goiter. Roentgen treatment for recurrent hyperthyroidism in 1945. Since hyperthyroidism still persisted, she was sent for I^{131} treatment. Typical hyperthyroidism without ocular symptoms. Small remnant of thyroid tissue palpable on the left side of the neck. Tracer tests gave the following results:

Date	Dose I ¹³¹ mC	$\bar{T}_{24}$	U_{24}
9.4.52	0.1	66	22
23.4.52	4 (therapy)	70	21
9.7.52	0.1	3	69
15.10.52	0.05	11	60
26.11.52	0.05	21	64
19.1.53	0.05	47	42
11.5.53	0.06	44	37
17.2.54	0.06	42	44
25.8.54	0.03	36	44

In this case the tracer tests indicated a very slow recovery of thyroid function, and seven months after the treatment the uptake was still considerably depressed. At the first follow-up in July, 1952, she was clinically euthyroid despite the low uptake, but at later examinations between October and December, there were obvious clinical signs of hypothyroidism which later on disappeared. She was not given substitution therapy.

A similar slow "recovery" of the thyroid function was noted in 9 of the 23 patients with transient hypothyroidism. Many patients had a very low uptake after about 2—3 months but at no time presented signs of hypothyroidism. Recovery of the thyroid function probably occurred so rapidly that there was no time for clinical signs of hypothyroidism to appear. This mechanism, however, can scarcely be the sole explanation of the discrepancy between the clinical picture and the tracer tests. For it was sometimes observed, perhaps mostly in toxic nodular goiters, that the uptake could be highly depressed for a long period without clinical hypothyroidism (Fig. 31 c, Chapter II). A conceivable explanation, mentioned previously, is that a goiter with a substantial hormone storage may continue to secrete hormone for a considerable time, despite its inability to take up new iodide for hormone synthesis.

A consideration of practical importance lies in the indications for substitution therapy during the first few months after treatment. The exogenous thyroid hormone inhibits the production of TSH, which might prevent the recovery or regeneration of the thyroid after the initial depression of its function, and thus increase the risk of hypothyroidism requiring permanent substitution therapy. In some cases with clinical signs of hypothyroidism the tracer tests afforded useful guidance for the management. If the tests after the initial depression of the function showed a rapid recovery, there was usually a good chance of the hypothyroidism being merely transient and also good reason to withhold substitution therapy. It is not possible to say in

what degree the early institution of thyroid medication will increase the risks of permanent hypothyroidism. In six of the patients with transient hypothyroidism, substitution therapy was given during an early period and it was later possible to withdraw the medication. It seems likely, however, that thyroid medication really inhibits the recovery of the thyroid function. The highest incidence of permanent hypothyroidism to be reported in a large series is 23 per cent (*Sweeney et al.* 331). These authors gave substitution therapy as soon as any clinical signs of hypothyroidism appeared. They also mentioned that later attempts to withdraw the thyroid medication almost invariably failed.

The time of the minimum uptake of I^{131} after a single treatment varied considerably but occurred most often between 1 and 4 months after treatment. The behaviour of the tracer test during the first 4—6 weeks was, however, incompletely studied because of the substantial activity remaining in the thyroid after the therapeutic dose. — If tracer tests with I^{131} are used during this period it is often necessary to give rather large tracer doses, which may interfere with the thyroid function and thus reduce the possibility of studying the functional changes in an individual patient. — It is probable that in some cases a minimum already occurred during this early period, though in many cases, studied with repeated tracer tests, it did not occur until 3—4 months after treatment (Figs. 33—36, Fig. 17 c). The variation in this respect was certainly due to several causes, as for instance the size of the irradiation dose and its protracted nature, the radiosensitivity of the thyroid tissue and the ability of that tissue to regenerate. The biologic mechanisms responsible for this early depression of the function and the rapid recovery are imperfectly known. Two explanations seem most likely:

1. During the irradiation reaction many thyroid cells are partially damaged and may recover when the reaction has subsided.
2. The surviving thyroid tissue will compensatorily increase its function, probably influenced by an increased thyrotropic stimulation.

A combination of these two mechanisms is likely. The very rapid recovery sometimes observed would, however, indicate that the first-named mechanism plays an important rôle. It is of interest to compare the course of events in another inflammatory reaction, *i.e.*, acute or subacute diffuse thyroiditis. In this condition the uptake of I^{131} is often severely depressed but returns to a normal level when the inflammation has subsided (*Werner et al.* 370; *Seed et al.* 297; *Robbins et al.* 271; *McConahey et al.* 191 a). Moreover clinical

signs of hypothyroidism are rare and there is a pronounced discrepancy between the uptake of I^{131} and other laboratory tests (BMR, SPI).

In one part of this series the BMR and serum cholesterol were studied parallel with the tracer tests. In patients with transient hypothyroidism a temporary decrease of BMR and increase of serum cholesterol to "hypothyroid" values were often noted, followed by a return to normal levels. Generally this phenomenon, however, was much more rarely seen and much less pronounced than was the case with the uptake of I^{131} . Repeated BMR determinations during the first few months after treatment have been reported by many authors (*Chapman et al.* 56—59; *Miller et al.* 207 a; *McCullagh et al.* 194, and others), and after successful treatment there has usually been a gradual decrease to normal values without transient depression to a subnormal level. *Williams et al.* (375) observed, however, in some cases a "rebound phenomenon" in the BMR values, with an early depression followed by a later increase. The level of protein-bound iodine in serum (SPI) will become adapted fairly rapidly to changes in the thyroid function, and it is therefore the laboratory test that, besides the tracer tests, has the greatest interest during an early phase after treatment. When this investigation was conducted the author unfortunately had no opportunity to perform this test at frequent intervals. Several authors have, however, reported the results of repeated SPI determinations after the treatment (*Chapman et al.* 57—59; *Miller et al.* 207 a, and others). Usually the values have gradually decreased to a normal level during the first few weeks or months (sometimes after the early increase previously mentioned) without passing a stage with subnormal values. The discrepancy in this respect between SPI and uptake of I^{131} supports the view that the gland may continue to release its stored hormone even when the uptake of new iodine is inhibited. In this respect too, there is a striking parallelism between the radioiodine treated gland and the acute diffuse thyroiditis; in the latter condition normal or supernormal SPI values have often been observed despite a very low uptake of I^{131} (*Robbins et al.* 271).

Several authors have observed that the uptake of I^{131} in patients with euthyroidism after radioiodine treatment is sometimes higher than that in normal subjects (*Soley et al.* 317; *Freedberg et al.* 93; *Myant* 217; *Horst et al.* 153, 155, 157; *Bauer* 23). It is difficult to determine the frequency of such "pathologic" values. There is no sharp distinction between the "normal" and "abnormal" ranges as regards the tracer tests. In the euthyroid controls

reported in Chapter I, 24-hour uptakes above 50 per cent and urinary excretion values below 30 per cent were fairly often observed. It is true that this series was not composed of normal subjects, but the results are closely consistent with the general impression gained from a very large number of diagnostic tracer tests performed in the laboratory. The best information on this subject could perhaps be obtained from a statistical analysis of a large series of normal subjects compared with a large number of patients euthyroid after I^{131} treatment. It seems to the author, however, to be a very difficult task to collect a really representative normal series which, as regards age, sex, environment, and dietary habits will be comparable with a group of radioiodine treated subjects. Another difficulty lies in the decision as to what really constitutes euthyroidism in some radioiodine treated subjects. Patients with very severe hyperthyroidism before the treatment may be so remarkably improved as to pass clinically as euthyroid, besides claiming to have no subjective signs of disease. Such cases may nevertheless have slight persistent hyperthyroidism, sometimes revealed only after prolonged detailed observation.

From this series the impression was gained that cases with pathologically increased uptake despite clinical euthyroidism were not very numerous. As will be seen from Fig. 39, the distribution of T_{24} and U_{24} was, with the exception of the first few months after the treatment, very similar to that in the control series (Fig. 5). The average values, too, agreed well with those in the controls. It was often observed, however, that the uptake after the early depression returned to a fairly high level, perhaps best classified as a high normal or "borderline" level. This observation was most commonly made in patients who, before the treatment, had tracer tests of extreme hyperthyroid type, and it occurred more often in diffuse toxic than in nodular toxic goiters (Fig. 33—36). A typical example of this kind is illustrated in Fig. 17 c, Chapter II. The case history is reported under the figure and here is merely implemented by the results of the tracer tests:

Date	Dose I^{131} mC	T_{24}	U_{24}
12.8.52	0.05	85	6
20.8.52	6 (therapy)	78	6
1.10.52	0.05	30	58
5.11.52	0.05	5	73
12.1.53	0.05	52	30
30.3.53	0.05	52	21
6.7.53	0.06	63	20
19.10.53	0.03	52	19
24.3.54	0.06	54	24
27.10.54	0.03	53	33

After the treatment the patient had a period of slight transient hypothyroidism from November, 1952 to February, 1953, but was then clinically euthyroid without any suspicion of hyperthyroidism, despite the rather high uptake of I^{131} . The values, however, never returned to the extreme type observed before treatment. The same observation was generally made in cases of this type.

Many cases that were euthyroid after radioiodine treatment still showed a rapid release of organic I^{131} from the gland. — In such cases a pathologically increased accumulation of I^{131} is more easily observable after early uptake measurements, while the 24-hour uptake may falsely reveal normal values (*Horst et al.* 153, 155, 157; *Bauer* 23).

In one part of the series the 3-hour uptake in the gland was measured. All patients seen for control and with clinically definite euthyroidism were, if possible, examined in this way during one period; and they had all been observed from 9 to 27 months after the last treatment. A total of 70 patients were examined. The results in these cases (B), in 44 euthyroid controls (A), and in a series of 23 consecutive cases with untreated demonstrable hyperthyroidism (C) are shown in Fig. 40. The distribution of the values was very similar in groups A and B, and the average 3-hour uptake was 18.8 per cent in the former group and 23.2 per cent in the latter, compared with 55.0 per cent in the untreated hyperthyroid patients (C). A few of the radioiodine treated patients had, however, remarkably high uptakes, and in one patient it was undoubtedly pathological. The 3-hour uptake was in this patient 58 per cent, while no value above 38 per cent was observed in the euthyroid controls; in this case, as in the other, there was no clinical suspicion of hyperthyroidism. The SPI was 7.8 and 7.5 μg per cent. High uptakes were more usual in patients examined at a rather early stage after the treatment. In Fig. 40, cases examined from 9 to 18 months after the treatment are marked with open circles and cases examined from 18 to 27 months are marked with black circles. All the high uptakes fall within the former group, and this is probably not accidental. For it was observed in several cases that the uptake after the initial depression returned to a fairly high level but then, over a long period, gradually diminished to a more "normal" level.

It was also of interest to study the initial "neck curves" after intravenous injection, using the technique previously described (*Larsson and Jonsson*, 179). For this study 55 consecutive patients seen for control and with undoubted euthyroidism one year or more after the last treatment were selected. The results are illustrated in Fig. 41, and the difference in H values during a 10-minute interval from one to eleven minutes has been used as an index

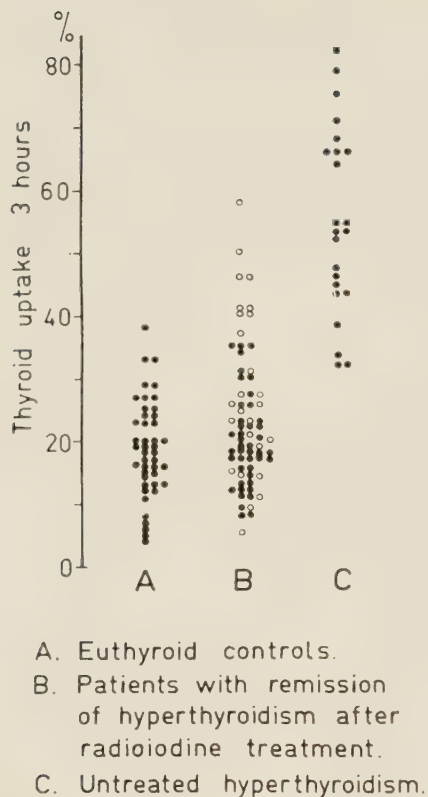


Fig. 40.

Fig. 40. Three-hours gland uptake of I^{131} in 44 euthyroid controls (A), 70 patients definitely euthyroid after radioiodine treatment (B), and 23 consecutive cases with untreated hyperthyroidism (C). Open circles denote patients examined 9–18 months after treatment and black circles patients examined 18–27 months after treatment.

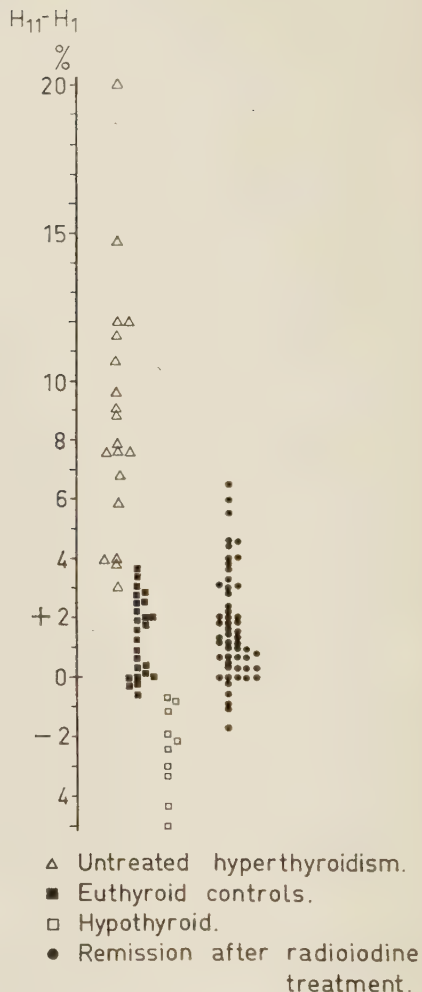


Fig. 41.

Fig. 41. Results of continuous registration over the thyroid without correction for neck background in 19 untreated hyperthyroid subjects, 25 euthyroid controls, 10 hypothyroid subjects, and 55 patients who were euthyroid one year or more after radioiodine treatment. The difference in the values during a 10-minute period from 1 to 10 minutes after the injection has been used as an index ($H_{11} - H_1$).

($H_{11} - H_1$). The average value in the 55 patients was 1.7 per cent, and in a group of 25 euthyroid controls 1.4 per cent. The average value in 19 untreated hyperthyroid patients was 8.9 per cent, and in 10 cases with hypothyroidism - 2.5 per cent. This test, too, revealed a few patients with remarkably rapid accumulation of I^{131} in the thyroid; however, no case with the extreme values often observed in untreated hyperthyroid subjects was noted.

As regards the early uptake measurements, it might be suggested that the cases with a rapid uptake had impaired organic binding but retained ability to concentrate inorganic iodide. This explanation is not likely. Patients with high 3-hour uptakes or rapid initial accumulation of I^{131} usually had, too, a high 24-hour uptake and a low 24-hour urinary excretion. In some cases there was a discrepancy between the results of the early uptake measurements and the 24-hour uptake. This discrepancy was, however, well explained by a rapid release of organic I^{131} from the thyroid, and all these cases had high values of PBI^{131} after 48 hours and a short biologic half life for I^{131} in the gland.

Pathologically increased ability to accumulate I^{131} despite clinical euthyroidism is, to judge from this series, not a matter of major practical importance. It does, however, undoubtedly occur and constitutes an interesting problem as regards the unknown biologic mechanisms involved. Since these patients are not likely, for a long period after the treatment, to have an iodine deficiency due to their diet, some change in their iodine metabolism must be assumed. Several hypotheses may be suggested. It may be a case of a "rebound phenomenon" similar to that seen in thyroid glands depleted of iodine after prolonged thiouracil or thiocyanate treatment; this explanation does not seem likely, since an increased uptake may be observed for a very long period after radioiodine treatment. The gland may produce an abnormal organic iodine compound that is rapidly metabolized and hence does not increase the SPI values (*Horst* 155). Lastly the whole explanation may lie in the peripheral iodine metabolism, a hypothesis that may receive some support from an investigation by *Burrows et al.* (45). These authors observed that the correlation between the uptake of I^{131} , on the one hand, and the clinical picture and SPI, on the other, was less good in patients who had received specific treatment (surgery, I^{131} or thiouracil) than in untreated euthyroid and hyperthyroid subjects. When they instead determined the average uptake of stable iodine in the gland, using a method previously described by *Stanley* (326), the correlation was fairly good in both treated and untreated subjects. The

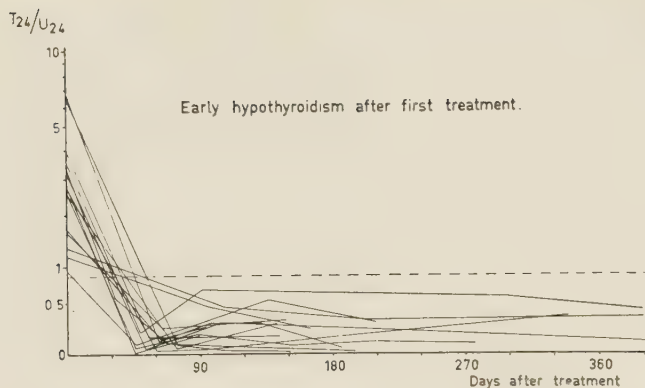


Fig. 42. The changes in the tracer tests (T_{24}/U_{24}), in 15 cases developing permanent hypothyroidism within the first year after a single treatment. Only patients examined with at least two tracer tests before the start of substitution therapy are included.

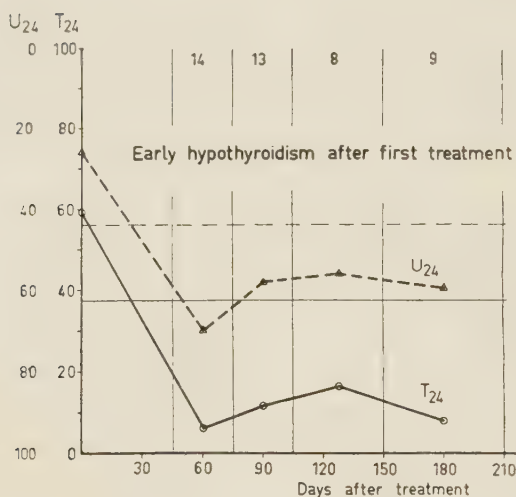


Fig. 43. Average values for T_{24} and U_{24} in 20 patients with permanent hypothyroidism developing within one year after the first treatment.

authors suggested that the iodine storage capacity might be reduced in treated thyroid glands and that the accumulation rate of I^{131} would therefore be more responsive to variations in iodine intake or in the peripheral utilization of the thyroid hormone. In treated patients with a high uptake despite clinical euthyroidism, one possibility would thus be that a larger fraction than usual of the organic iodine may be discharged from the body (see formula 1, Chapter I).

Cases with Permanent Hypothyroidism. — Hypothyroidism appeared usually during the first half year after the treatment, but in a few patients it developed only after a fairly long time. In the following, hypothyroidism

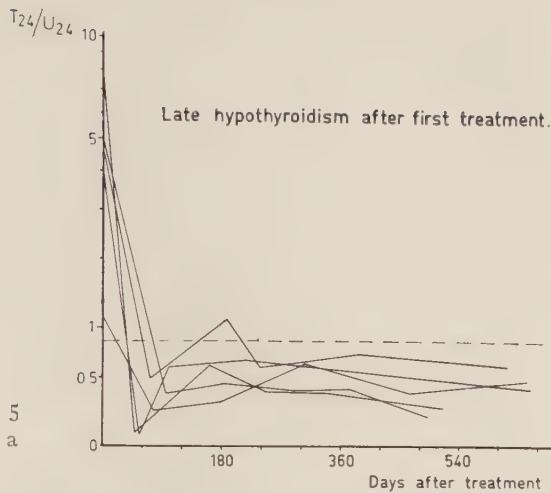


Fig. 44. The tracer tests (T_{24}/U_{24}) in 5 patients with late hypothyroidism after a single treatment.

appearing during the first year is classified as “early”. In almost all cases of this type the first tracer test about 6—14 weeks after treatment revealed a very low uptake (Figs. 42, 49). The patients often had, at that time, no clinical signs of hypothyroidism, though these gradually appeared during the following months. In the patients who underwent several follow-up tracer tests it was often noted that the uptake later increased slightly, without, however, reaching a normal level, indicating an insufficient recovery. If the patient was studied further, before substitution therapy was started, the uptake of I^{131} usually decreased again. In Fig. 43 the average values for T_{24} and U_{24} at varying intervals after the treatment are illustrated in respect of 20 cases with “early” hypothyroidism after the first treatment. In Fig. 42 the changes in the tracer test (T_{24}/U_{24}) in the individual cases after the first treatment are demonstrated; only the 15 cases where more than one tracer test was made before the start of substitution therapy are included. Even the cases that developed hypothyroidism only after re-treatment, usually had a marked depression of the uptake after about 2—3 months, as will be seen from Fig. 49.

In a total of 10 cases hyperthyroidism did not appear until a fairly long time after the treatment, and these patients were still clinically euthyroid one year after the last treatment. Fig. 44 shows the results of the tracer tests in the five cases with late hypothyroidism after a single treatment; following the early depression the uptake increased to a normal or low normal level but

later decreased again concomitantly with the gradual appearance of clinical hypothyroidism. The five cases with late hypothyroidism only after re-treatment were also examined about 2—3 months after the last treatment at which time they showed a fairly normal uptake (23—42 per cent), and only after a long time did it decrease to a low level.

The observation period in this series is too short to permit of any conclusions as to the incidence of late hypothyroidism; cases have been reported in which hypothyroidism has appeared after several years. One patient in this series was clinically euthyroid up to 2 years after the last treatment but, when followed up half a year later, showed obvious signs of hypothyroidism. The pathogenesis of early and of late hypothyroidism may differ somewhat, as in other early and late irradiation injuries, the former being due to extensive irreparable cell damage and the latter to slowly developing late sequelae as fibrosis, vascular changes and atrophy.

Normal or high uptake of I^{131} has been reported in patients with definite hypothyroidism after radioiodine treatment (*Soley et al.* 317). If slight transient hypothyroidism be excluded, a high uptake was never observed in patients with hypothyroidism in this series. Two of the patients with slowly developing late hypothyroidism had a normal or low normal uptake when substitution therapy started, and one of these cases is briefly reported.

A.S.A.L. R. 378/53. Woman, 45, with recurrent slight hyperthyroidism after previous operation for diffuse toxic goiter. BMR before treatment + 30 per cent.

Date	Dose I^{131} mC	T_{24}	U_{24}
19.1.53	0.05	69 %	18 %
2.2.53	4 (therapy)	69 %	> 8 % (incomplete)
30.3.53	0.05	5 %	73 %
11.5.53	0.06	32 %	54 %
7.9.53	0.06	28 %	43 %
12.5.54	0.03	29 %	58 %
17.11.54	0.06	27 %	66 %

After the treatment she had transient signs of hypothyroidism from March to June, 1953, but was later euthyroid or possibly very slightly hypothyroid. BMR at the end of February, 1954, was - 8 per cent and on May 8, 1954, + 1 per cent. From August, 1954, she showed increasing signs of hypothyroidism and, when followed up in November, 1954, had undoubted clinical signs of hypothyroidism, with fatigue, apathy, increase in weight, and palpebral edema. BMR - 17 per cent; serum cholesterol 309 mg per cent; and SPI 6.6 μ g per cent. Despite the laboratory values, she received substitution therapy as the clinical signs of hypothyroidism were manifest.

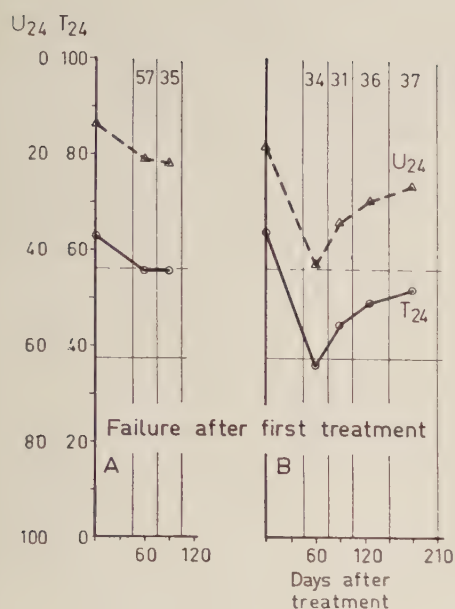


Fig. 45.

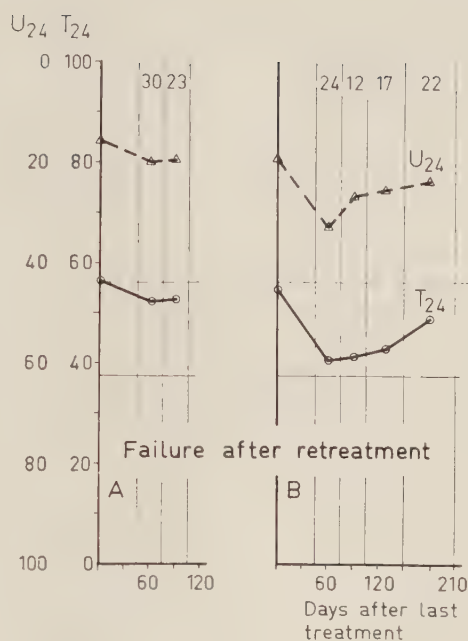


Fig. 46.

Fig. 45. Average values for T_{24} and U_{24} in patients requiring further treatment after the first treatment. A. Patients re-treated within 120 days (84 cases). B. Patients observed at least 120 days before re-treatment (66 cases).

Fig. 46. Average values for T_{24} and U_{24} in patients requiring further treatment after re-treatment. A. Re-treated within 120 days (46 treatments). B. Observed at least 120 days before re-treatment (40 treatments).

In most cases of myxedema (postsurgical, spontaneous, pituitary) the accumulation of I^{131} already proceeds very slowly during the initial phase after the administration, if there is any uptake at all in the thyroid. This type is characterized by an "overall" impairment of the function, due either to a reduced mass of thyroid tissue or diminished pituitary stimulation. Another type of uptake curve is seen in thiouracil myxedema (under continued thiouracil treatment) and in some goitrous cretins; namely, a rapid initial uptake but a low 24-hours uptake, due to retained iodide concentrating capacity but impaired organic binding of iodine. The uptake curves in post-radioiodine hypothyroidism are referable to the first of these types — a fact which has hardly been questioned. In seven patients with post-radioiodine hypothyroidism continuous registration was done after intravenous injection

Failure after first treatment

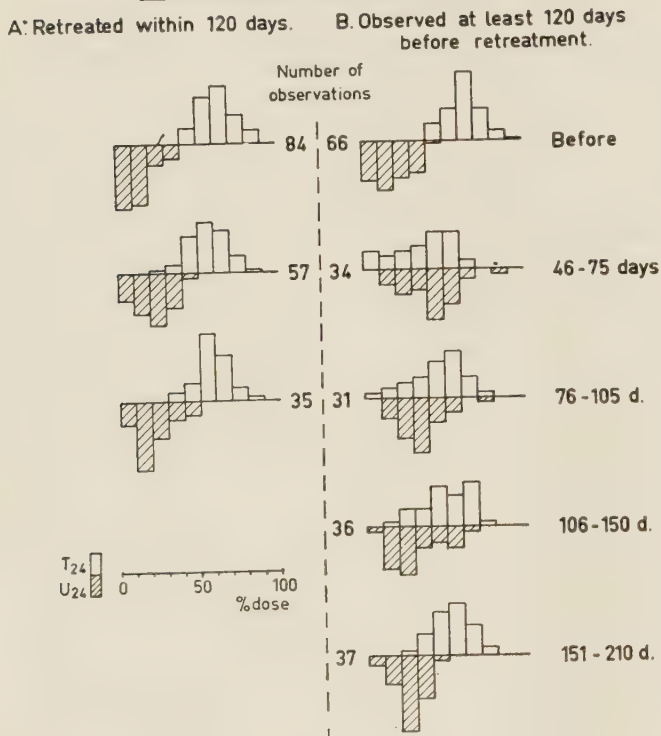


Fig. 47. Distribution diagrams for T_{24} and U_{24} in the same patients as in Fig. 45.

and all of them revealed typical slowly descending “neck curves” during the initial period, due to the diminishing body background and the slow uptake in the thyroid; rapid initial accumulation as seen in thiouracil treated subjects was in no case observed.

Failures. — The average values of T_{24} and U_{24} in the cases that required further treatment are shown in Figs. 45 and 46. The cases have been divided into two groups: (A) cases re-treated within 120 days, and (B) cases observed at least 120 days before re-treatment.

In group A the patients were usually re-treated after only 2—3 months or so. Many of them were at that time more or less improved, but most cases still had obvious clinical signs of hyperthyroidism. The uptake of I^{131} in the gland was still pathologically high, even if it had often decreased somewhat compared with the pre-treatment values (Figs. 45, 46, 47). Several examples of this kind are reported in Chapter II (Figs. 13, 18, 20, 22, 23, 31).

Group B includes a large number of patients with transient improvements and even transient remissions. Most of them had, after 2—3 months, a considerable depression of the uptake, sometimes even to subnormal levels just as in the group with definite remissions. During the next few months the uptake increased again to pathologically high levels, concurrently with an increase or reappearance of hyperthyroid symptoms. The typical transient depression of the thyroid function in these cases is clearly observable in the average values in Figs. 45 and 46 and the distribution diagrams in Fig. 47. The following case may serve as an example of this group:

D.H.B. R. 7981/52. Woman, 39, operated on in 1945 for diffuse toxic goiter. Treated from 1947 to 1951 with methylthiouracil for recurrent hyperthyroidism, with full remission. After withdrawal of thiouracil, gradually increasing hyperthyroidism once more. The last BMR values before radioiodine treatment were about +45 per cent. Small diffuse goiter.

Date	Dose I ¹³¹ mC	T ₂₄	U ₂₄
26.11.53	0.06	76	17
19.3.53	3 (therapy)	77	23
4.5.53	0.07	16	58
15.6.53	0.06	45	30
14.9.53	0.06	60	19

She was greatly improved after the first treatment and clinically euthyroid at follow-ups in May and June, 1953; BMR, June 16, +23 per cent. During the next few months she gradually deteriorated again, with increasing signs of hyperthyroidism, and at a follow-up in September, 1953, was definitely hyperthyroid; BMR +41 per cent. She received further radioiodine treatment, followed by a definite remission.

The occurrence of transient improvements or remissions necessitates a detailed clinical follow-up of the patients for several months, and the treatment cannot be regarded as concluded until full remission has been observed for at least 6—12 months after the last treatment.

As previously mentioned, the capacity of the thyroid to accumulate I¹³¹ will in some cases increase, after the early depression, to a strikingly high level even though the patient may still be euthyroid, to judge from clinical and other laboratory data. If the case just described (DHB) and the one reported on page 104 (MK) are compared, it will be found that the tracer tests in both cases behaved very similarly after the treatment; namely, first a depression of the uptake, then an increase to a pathologically high level. Nevertheless the clinical findings were quite different. These observations

call for circumspection in evaluation of the tracer tests during this later phase after the treatment. Such pathological tests were, however, rarely seen in patients who were still euthyroid, and tests of extreme "hyperthyroid" type as in some untreated subjects, were never observed. From the practical point of view it may thus be said that in clinically ambiguous cases a pathologically high accumulation of I^{131} will at least suggest that the patient is still hyperthyroid.

3. Prognostic Importance of Early Tracer Tests

The capacity of the thyroid to accumulate I^{131} , as pointed out above, may be expected to change more rapidly after treatment, than the clinical picture and those laboratory tests which reflect the peripheral action of the thyroid hormone. Tracer tests may therefore provide information of prognostic value at a stage when the clinical picture is still obscure.

Before this matter is discussed, however, another more noteworthy observation will be reported; namely, with the treatment technique used, the results of pre-treatment tracer tests had a definite correlation to the clinical course after a single treatment. Fig. 48 shows the values for $\bar{T}_{24}/\bar{U}_{24}$ before and after the first treatment and re-treatment. The cases have been divided into four groups: patients requiring further treatment and re-treated within 120 days (A), or observed at least 120 days before re-treatment (B); patients definitely euthyroid (C), and patients with permanent hypothyroidism (D) after the actual treatment. (The four cases in which hypothyroidism was intentionally caused due to congestive heart failure are excluded. The same applies to the 10 cases with "late" hypothyroidism; however, it makes no difference to the general picture whether they be referred to the hypothyroid group or, perhaps more correctly, to the euthyroid group.)

These four groups represent, on the average, different degrees of response to the treatment. In group A the response was fairly slight and the cases were early re-treated. In group B the retreatment was delayed, usually because of transient improvement and transient depression of the uptake. Group C represents the ideal response and group D too great a response. As shown in Fig. 48 and Table 2, the value for $\bar{T}_{24}/\bar{U}_{24}$ was highest before the treatment in group A and then fell progressively with increasing therapeutic effect. These differences are certainly not due to chance, perhaps with the exception of group D, where the number of observations was small. From Table 2 it

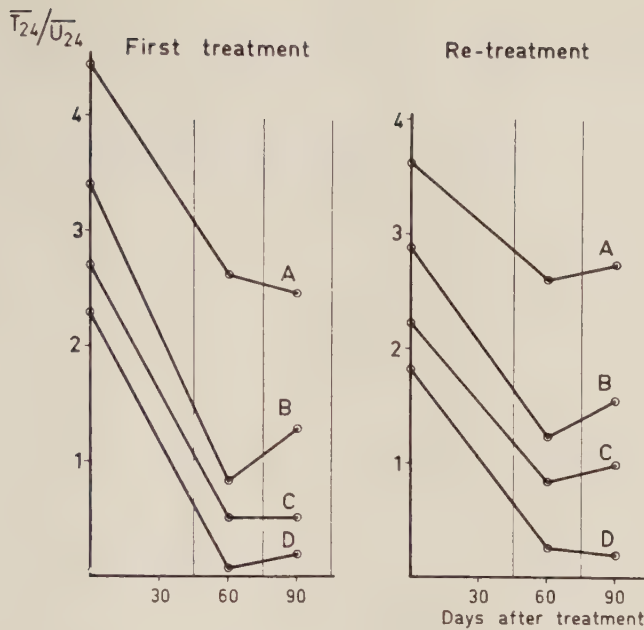


Fig. 48. Values of T_{24}/U_{24} before and after the first treatment and the re-treatment. A. Cases requiring further treatment and re-treated within 120 days. B. Cases requiring further treatment and observed at least 120 days before re-treatment. C. Cases with permanent euthyroidism. D. Cases with permanent hypothyroidism.

Table 2

Group	First treatment				Re-treatment			
	Number of observations	$\bar{T}_{24}$	$\bar{U}_{24}$	$\bar{T}_{24}/\bar{U}_{24}$	Number of observations	$\bar{T}_{24}$	$\bar{U}_{24}$	$\bar{T}_{24}/\bar{U}_{24}$
A	84	62.6	14.1	4.44	46	56.4	15.6	3.62
B	66	63.8	18.8	3.39	40	54.9	19.0	2.88
C	125	60.6	22.4	2.71	124	53.5	24.1	2.22
D	20	59.2	25.8	2.3	11	55.0	30.0	1.83

will be seen that there was a pronounced difference as to U_{24} in the various groups but no great difference in respect of T_{24} . If the series is grouped with regard to the value for U_{24} before the treatment, a striking correlation will be found between the magnitude of U_{24} and the incidence of definite remissions after the treatment, as shown in Table 3. If the U_{24} value before treat-

Table 3

U_{24}	First treatment		Re-treatment	
	Number of observations	Percentage of definite remission	Number of observations	Percentage of definite remission
$0 < U_{24} < 10$	69	27.5 %	28	28.5 %
$10 \leq U_{24} < 20$	96	46 %	70	50 %
$20 \leq U_{24} < 30$	67	62.5 %	74	66 %
$30 \leq U_{24}$	68	67.5 %	54	85 %

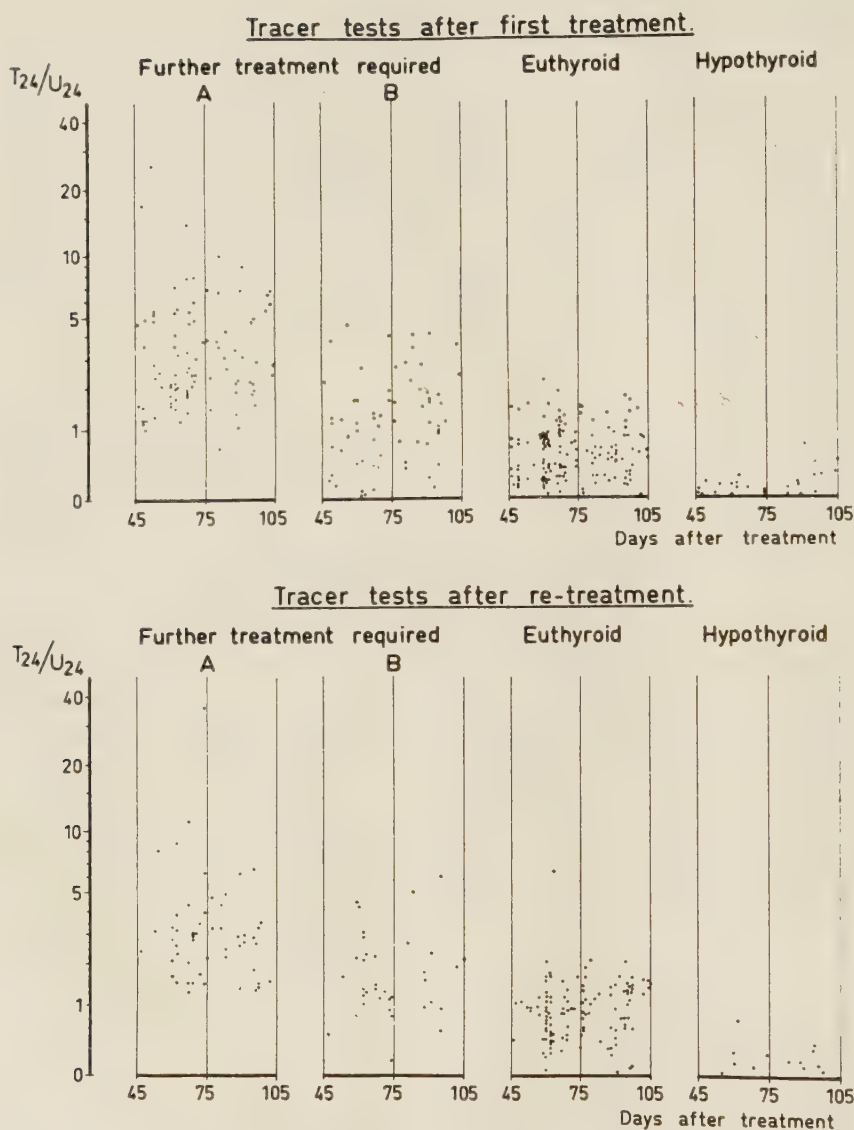
ment was 30 per cent or more, the chances of being cured by this single treatment were thus two or three times greater than if that value was below 10 per cent. Many investigators have used the same simple treatment technique as in this series, *i.e.*, they have mainly adjusted the administered therapeutic activity to the size of the thyroid; but the writer has seen no previous reference to the above-mentioned correlation. Some observations of similar character have, however, been reported. *Rall et al.* (255) observed that patients with a high blood level of I^{131} after 48 hours showed fewer remissions after a single treatment, when the therapeutic I^{131} activity only was adjusted to the size of the thyroid. *Miller et al.* (207 a) found that it often took longer to cure patients who before the treatment had unusually high SPI values. *Crile et al.* (69) stated that patients with a BMR exceeding +50 per cent required, on the average, double the total activities for remission, as compared with patients with BMR below +50 per cent. These observations may have at least two explanations:

1. The aforementioned group of patients (low U_{24} , high plasma level of I^{131} after 48 hours, high BMR, high SPI) may have, on the average, a shorter EHL for I^{131} in the thyroid and therefore receive lower irradiation doses. This mechanism is evident in the patients with high blood concentrations of I^{131} after 48 hours. It is also a likely explanation of the correlation between U_{24} and the therapeutic results noted in this series. No similar correlation was detectable in the case of T_{24} . If Table 2 is studied, it will be found that the sum of T_{24} and U_{24} was lowest in group A, which had the poorest responses, and it gradually increased in the other groups. This suggests that the cases with a poor response had, on the average, a more rapid release

of organic I^{131} from the gland, so that more of it was circulating in the body after 24 hours. It also seems likely that cases with severe hyperthyroidism, high BMR and high SPI have a relatively short EHL. The observation made by *Miller et al.* cannot, however, be fully explained by this mechanism, for those authors really used an average dose calculation after estimation of EHL.

2. A second possibility would be that all the groups mentioned represent, on the average, severer forms of hyperthyroidism and that, due to the strongly hyperactive nature of the thyroid tissue, a more extensive destruction of the gland will be required for definite remission.

If the first explanation is correct, the simple dosimetry used in this investigation must be regarded as unsatisfactory. When the investigation started we were greatly influenced by the report from *Miller and Sheline* (209), who found that the "preselected" average dose was not better correlated to the result than was the administered activity per gram thyroid tissue. However, their conclusions are not necessarily correct. The number of patients may have been too small, and it is also possible that the errors in estimation of the thyroid weight were so large as to spoil the correlation. Several later authors (*Blomfield et al.* 36, 37; *Horst* 151, 153, 155, 157) have emphasized the importance of an average dose calculation, without, however, as yet reporting any evidence of a close correlation between the calculated dose and the clinical results. With the methods now available for estimation of the thyroid size (directional scintillation counters), a detailed average dose calculation would possibly have more meaning. Since 1954 we have in most cases calculated the average dose, at all events for the first treatment, after approximate estimation of EHL from 1 to 8 days and clinical estimation of the thyroid size; in goiters difficult to palpate, often supplemented by delineation with a directional scintillation counter. This series is too small, and the observation time too short, for any conclusions to be drawn. Due to the biologic variations a detailed average dose calculation, however, is certainly not the whole solution of the problem. It is not unlikely that multiple treatments with the guidance of early tracer tests after each treatment, would be the best alternative in many patients — a matter that will be further discussed below. But in any case the reported correlation between the result of the preceding tracer test and the effect of treatment is of practical interest and of value for the management of the patients if a treatment technique similar to that in this investigation is used.



Figs. 49 and 50. Results of tracer tests (T_{24}/U_{24}) performed from 46 to 105 days after the first treatment (Fig. 49) and after re-treatment (Fig. 50).

That early tracer tests after the treatment will afford useful prognostic information is obvious. Yet the information obtained is relative. One patient may have a very low uptake after about 2—3 months without definite remission; another may still have, at that time, a tracer test of “hyperthyroid”

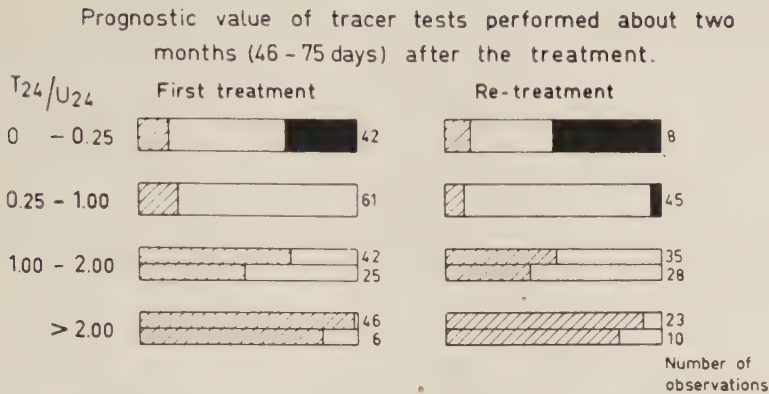


Fig. 51. Prognostic value of tracer tests performed from 46 to 75 days after the treatment. Black columns: permanent hypothyroidism. White columns: permanent euthyroidism. Obliquely lined: patients requiring further treatment. The two lower columns have been divided into two parts, the upper one representing all the cases and the lower on only those who were observed at least 120 days before re-treatment.

type, yet show a remission without further treatment. These variations are illustrated in Figs. 49 and 50, which show the results of tracer tests (T_{24}/U_{24}) 46—105 days after treatment, with the same grouping of patients as before. On the whole, however, the correlation between the tracer tests after 2—3 months and the clinical results was so good that these tests undoubtedly afford very useful guidance. In Fig. 51 the series is grouped with regard to the value for T_{24}/U_{24} about 2 months (46—75 days) after treatment. If the results after the first treatment and after re-treatment are added, the following correlation will be obtained.

T_{24}/U_{24}	Number of observations	Further treatment required	Euthyroid	Hypothyroid
0—0.25	50	7	25	18
0.25—1.00	106	15	89	2
1.00—2.00	77 (53)	44 (23)	30 (30)	0 (0)
> 2	69 (16)	66 (13)	3 (3)	0 (0)

(In the figures in parentheses, patients re-treated within 120 days are excluded.)

The findings may be summarized as follows.

1. If T_{24}/U_{24} was depressed below 0.25, half the number became euthyroid, about 35 per cent developed permanent hypothyroidism, and about 15 per cent showed a transient effect and later required further treatment.

2. If T_{24}/U_{24} had a value between 0.25 and 1.00, most patients became euthyroid, about 15 per cent later required further treatment, and only 2 per cent developed permanent hypothyroidism.

3. If T_{24}/U_{24} was 1.00—2.00, about half the number required further treatment and the other half became euthyroid. If T_{24}/U_{24} was more than 2.00, most patients required further treatment. Permanent hypothyroidism did not occur in the last two groups. (The 10 cases with late hypothyroidism are not included in the tabulation above. If they be included, the incidence of hypothyroidism in the group with T_{24}/U_{24} from 0.25—1.00 will somewhat increase.)

Conclusions 1 and 2 are fairly safe as patients in these groups had a sufficiently long observation period before any eventual re-treatment. The results suggest that in a patient where the accumulation of I^{131} is normal or subnormal, re-treatment will never be indicated at that time, regardless of the clinical picture (unless permanent hypothyroidism is desired for special reasons). If the uptake after about 2 months is very low, careful follow-up will be indicated in order to prevent the development of pronounced myxedema before substitution therapy is started.

To conclusion 3, definite objections may be raised. Many of the patients in these groups were re-treated at an early stage, often with the guidance of the tracer test. It is not impossible that several of these patients would later have had remissions even without further treatment. The policy as regards re-treatment varies considerably in different investigations. Some authors have re-treated the patients after only three weeks; others have waited as long as 6—12 months. *Chapman et al.* (58), on the basis of experience with a large series, advised against re-treatment, as a rule, until about 6—12 months had elapsed, and noted in some cases a progressive depression of the thyroid function during a very long period after a single treatment. That the last-named may occur is clearly demonstrated by the cases with late hypothyroidism. Yet the present writer, with experience of this series, finds the view expressed by *Chapman et al.* on the whole difficult to understand. Many cases were observed with only transient improvements and requiring a fairly

large number of treatments before definite remission occurred. It is possible that these different opinions are partly due to varying composition of the series. The present series contained a very large proportion of cases where previous treatment had failed (surgery, thiouracil), and it may represent, on the average, a selected series of cases more resistant to therapy.

On the contrary, the impression was gained in this series that many cases would have been better helped by earlier re-treatment than was actually used. If, for instance, the first two treatments failed, it took at least 6 months from the start of treatment for the patient to show full remission if re-treatment was only given every second month. *Myant* (217) showed clearly that the results of tracer tests performed as early as 3 weeks after the treatment, afforded valuable prognostic information. In this series tracer tests were sometimes done from 20 to 40 days after the treatment, and the results are illustrated in Fig. 52. Only U_{24} was estimated in many of these cases, due to the high activity remaining in the thyroid (to increase the series, cases investigated in this way from January to June, 1954 have been included). As shown in the figure, there was, even at this early stage, a good correlation between the tracer test and the prognosis. In Fig. 53, eleven cases studied by tracer tests every second week during the initial period after treatment are illustrated. It is of interest to note that U_{24} had definitely increased in two of the patients after only two weeks; one of them had a definite remission and the other merely a transient remission. In two of the cases with definite remissions, U_{24} was still low after 2 weeks but later started to increase. In most cases without remission, U_{24} remained low throughout the observation period. The series is of course too small for any far-reaching conclusions. Bearing in mind the protracted nature of I^{131} treatment and the latent period between irradiation and biologic reaction it seems improbable, however, that tracer tests after only 2 weeks will afford any reliable prognostic information. That useful information may already be obtained after 3—4 weeks is, however, well supported both by the findings of *Myant* (217) and by the above investigations. The tests after about 2 months probably yield more reliable information, but in cases with severe hyperthyroidism or severe complicating diseases, where prompt control of the disease is essential, tracer tests after only one month, followed by re-treatment if indicated, may be the method of choice. At that early stage large tracer doses are often required because of the activity remaining in the thyroid after the therapeutic dose. In the above-mentioned investigation where only U_{24} was used, activities up

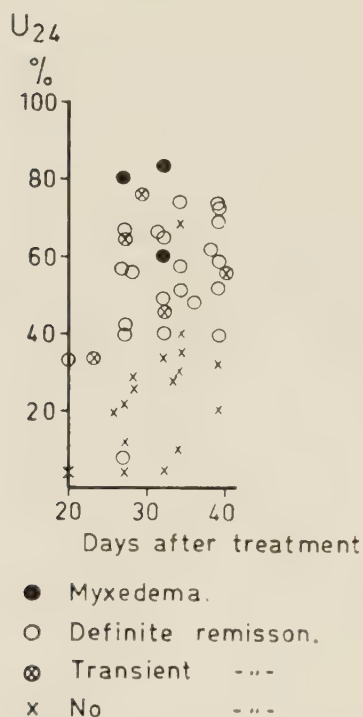


Fig. 52. Prognostic value of tracer tests (U_{24}) performed from 20 to 40 days after the first treatment.

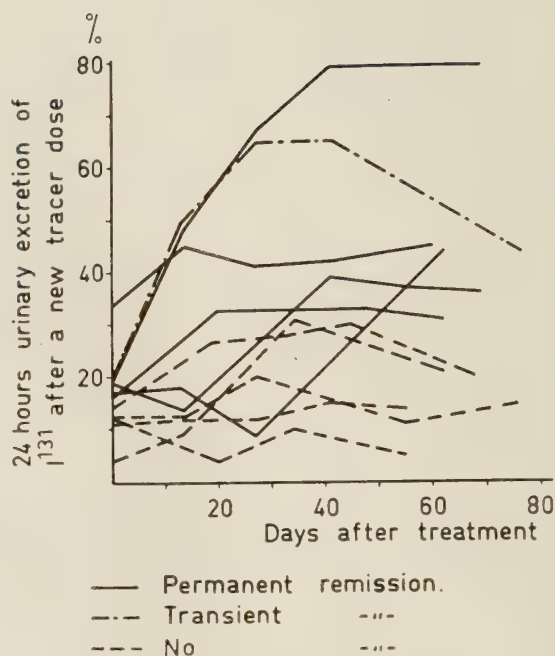


Fig. 53. Results tracer tests (U_{24}) in eleven patients who underwent one tracer tests every second week during the initial period after the treatment.

to 0.6 mC were sometimes given after 2 weeks, and up to 0.1—0.2 mC after 4 weeks, in order to correct for persisting activity. — Despite measurements 2 hours after administration, which facilitates the correction, *Myant* sometimes had to give doses up to 0.5 mC. Such tracer doses are in many cases justified, but certainly they often have a definite influence on the thyroid function, which lessens the possibility of studying the functional changes in an individual patient. I^{132} (half-life 2.33 hours) has recently been introduced for thyroid studies (*Stang et al.* 325; *Hanbury et al.* 132). Due to the short half-life, fairly high activities can be given without delivering a large irradiation dose in the thyroid. Combined with the previously described technique of continuous registration after intravenous injection (*Larsson and Jonsson*, 179), it seems to be an ideal procedure when the amount of I^{131} remaining in the thyroid is high, and has recently been used in this way at our laboratory. For a period as short as 10—15 minutes the change in the remaining activity

will be negligible and it is also possible to give sufficiently high activities for reliable measurements, despite the remaining activity and without substantially adding to the irradiation dose.

The behaviour of the therapeutic dose itself may also afford information of prognostic importance. *Schaffner et al.* (289) studied the disappearance rate of the therapeutic activity in the thyroid and found that it increased after some weeks in cases with a good therapeutic response. It is not clear what interpretation should be placed on this finding. The effect seems to be too late to be explained by the release of labelled thyroid proteins. An increased thyrotropic stimulation due to the decreased level of circulating thyroid hormone is perhaps a more likely explanation. Another possibility of obtaining prognostic information from the therapeutic dose would be to analyse the serum I^{131} fractions during the initial period after treatment. It seems possible that the release of labelled thyroid proteins may in some way be correlated to the therapeutic effect of the treatment.

4. The Organic Binding of I^{131} in the Thyroid

Radioiodine treatment is in most respects analogous with surgical treatment. Both methods imply an "overall" depression of the thyroid function by reducing the mass of active thyroid tissue, and the main difference from the physiologic point of view lies in the time relations for this depression. Another difference may, however, exist; namely, that the irradiation damages the cells only partially. Such a mechanism is most likely during an early phase after the treatment, before the restitution after the irradiation reaction has concluded. It has been suggested that the irradiation might damage the partial functions of the thyroid cells to a varying degree, thus inducing changes of a more qualitative nature. Very little is known about this mechanism, or indeed whether it exists at all.

Myant (218) treated four thyrotoxic patients with multiple small doses of I^{131} administered intravenously once weekly. Following each dose he determined the neck/thigh ratio after 2 hours, the 24 hours gland uptake, and the secondary rise in the plasma radioiodine concentration; this rise was regarded as an expression of the rate at which labelled hormone was secreted from the thyroid. After a few weeks he found a progressive and fairly parallel depression of all these values; in one of the subjects, however, the secondary rise of the plasma radioiodine concentrations was depressed at a somewhat earlier

stage than the uptake, which fact might suggest that the mechanism concerned in the secretion of hormone was more radiosensitive than that responsible for iodine uptake. There was throughout a close parallelism between the neck/thigh ratio after two hours and the 24 hours uptake. If the iodide-concentrating mechanism had been less impaired than the ability of the gland to bind iodine organically, a discrepancy between these two values could have been expected. *Myant*, on the contrary, suggested that the iodide-concentrating mechanism was primarily affected and that the uptake was diminished because less iodide was available in the gland for organic binding.

Horst et al (157) observed, as previously mentioned, that some radioiodine treated subjects, despite clinical euthyroidism after prolonged observation, had a pathologically increased thyroid accumulation of I^{131} and also an increased disappearance rate of I^{131} in the gland. They gave a few patients of this type 2 grams of potassium iodide two hours after administration of the tracer dose and found no rapid decrease of thyroid radioiodine, indicating that the bulk of it was organically bound. The high disappearance rate of I^{131} from the gland was certainly due to a rapid secretion of hormonal radioiodine, and these cases also had high PBI^{131} values.

Neither of the above investigations, one conducted at a very early stage and one at a late stage after treatment, supports the view that impaired organic binding of iodine, with retained iodide-concentrating capacity, is an important mechanism after radioiodine treatment. *Kirkland* (173), however, reported that about two months after treatment such a mechanism could nearly always be observed; it was transient in some cases, but in others could be observed for several months after treatment. He gave the tracer dose by mouth and measured the uptake after about 1 and 3 hours; after 3 hours he administered 2 gm sodium thiocyanate on an empty stomach and studied the uptake in the thyroid for a further two hours with repeated measurements. He found that in radioiodine treated subjects the uptake curves were often of the so-called "injury type" as in thiouracil treatment; *i.e.*, the 3 hours uptake was remarkably low compared with the one-hour uptake, due to impaired organic binding of radioiodine in the thyroid. The releasability of the thyroid radioiodine by thiocyanate was studied in 20 untreated hyperthyroid or euthyroid subjects and in 10 patients with remissions after radioiodine treatment, given at least 2 months previously. In the untreated subjects only insignificant amounts were releasable with thiocyanate and the thyroid radioiodine diminished, on the average, by only 3.4 per cent of the value

before thiocyanate administration. In the treated subjects from about 20 to 100 per cent of the thyroid radioiodine was releasable, with an average of 54.1 per cent. If correct, this finding is most remarkable and also of major practical importance, for it would definitely reduce the reliability of tracer tests based on early uptake measurements during this period (for instance, the one or two hour gland uptake, thyroid clearance, neck/thigh ratio, "initial neck curves"). This does not accord with the writer's experience, nor with that of other investigators (*Myant* 217, 218; *Ansell et al.* 9; *Horst et al.* 151, 153, 155, 157). The findings of *Kirkland* with regard to the type of uptake curves might be explained by technical shortcomings. If the accumulation of I^{131} is low, as it often is in patients with remissions after 2 months, the measured one-hour uptake might be misleadingly high compared with the 3 hours uptake, due to the relatively great influence on the neck background values unless an adequate technique for correction is used. The findings after thiocyanate administration cannot, however, be explained in this way; and the proportion of I^{131} released from the gland was in many cases so high that there can be no doubt about the observation.

The above investigations are, therefore, somewhat contradictory. In order to throw further light on this state of affairs, the following investigation was conducted, using a detailed technique described in Chapter I (page 31). It was expected that simultaneous recording of the thyroid uptake curves and the plasma concentration curves would give more reliable information.

A total of 18 radioiodine treated subjects and 17 controls were examined and selected according to the following principles.

Ten radioiodine treated subjects were examined at a relatively early stage after treatment (2—4 months). Five of these patients had full remissions and remained euthyroid at the subsequent follow-ups (curves 20, 22, 26, 27, 24). Two of the patients (21, 23) had transient remissions at the time of the investigation but later required further treatment. Three patients were improved but still hyperthyroid (18, 19, 25). In all patients there was a definite therapeutic effect, to judge from clinical data and from the tracer test before and after treatment.

Eight patients were examined from 7 to 30 months after radioiodine treatment. One patient had manifest clinical hypothyroidism but a fairly normal uptake, and was therefore selected (curve 34). One patient was improved but still hyperthyroid (32). The other patients were clinically euthyroid (28, 29, 30, 31, 33, 35). Three patients were selected because they had, notwithstanding clinical euthyroidism, a strikingly rapid accumulation of I^{131} in the gland (28, 29, 30).

Eleven untreated controls were investigated. Five of them were hyperthyroid (7, 8, 9, 10, 11) and six euthyroid (12, 13, 14, 15, 16, 17).

Nine tests were performed in thiouracil treated patients, six of them in hyperthyroid subjects (1, 2, 3, 4, 5, 6) and three in euthyroid controls (36, 37, 38). All of them had

been treated for several days with propyl- or methylthiouracil and received the last dose within one hour before the tracer test. The size of the last dose was 50—150 mg propylthiouracil or 100 mg methylthiouracil. Two patients were examined twice after different doses (curves 1 and 2; 3 and 6). Thiocyanate was given only at the last examination. This series is only reported for purposes of comparison, and the details of the thiouracil treatment are therefore omitted.

The technique for neck background correction was the same as that described in Chapter I, with the exception of cases 6, 10 and 15 which were examined at an earlier period. In these cases parallel measurements were done over the neck and the thigh. When the thigh curve had reached a negative slope it was extrapolated back to zero time on a semilogarithmic scale, then multiplied by a correction factor in the same way as the neck background curves. Due to the steeper initial slope of the neck background curve, this technique will probably give some overcorrection. In two of the patients (12, 20) the blood sampling failed, and in these cases only the thyroid curves and the effect of thiocyanate are reported.

The thyroid uptake curves during the first 2 hours after the injection were plotted against the square root of time. This method was used by *Astwood* and *Stanley* (18, 327), who showed that the curves, when plotted in this way, usually had a linear course during the initial period in untreated hyper- and euthyroid subjects. In cases where the organic binding of I^{131} was abolished by drugs of thiouracil type, an early deviation from the linear course was usually observed. Since the technique for estimation of the thyroid uptake curves differed in the present series, a group of untreated hyperthyroid and euthyroid subjects is illustrated in Fig. 54. Most curves were fairly linear; early deviation from a linear course was noted especially in hyperthyroid subjects with a rapid accumulation of I^{131} — an observation also made by *Astwood et al.* In Fig. 55 the thyroid uptake curves in the thiouracil treated subjects are plotted in the same way. Here most curves early show a deviation from the linear course, and two of the curves even have an early maximum (3 and 6). Figs. 56 and 57 show the uptake curves in the radioiodine treated patients. The type of these curves accords, on the whole, with that observed in the untreated subjects. Early deviation from the linear course is also noted here in some cases with a rapid accumulation of I^{131} , which fact cannot be accounted any especial significance. The other curves are fairly linear during the early period. One of the curves (25, Fig. 56) possibly bears a slight resemblance to the "injury type", but extreme curves similar to those in the thiouracil treated subjects were not observed.

In Figs. 58—61, the results of thiocyanate administration are shown. Two grams of sodium thiocyanate was given on an empty stomach 125 minutes after injection of the tracer dose, and the thyroid curves were studied for

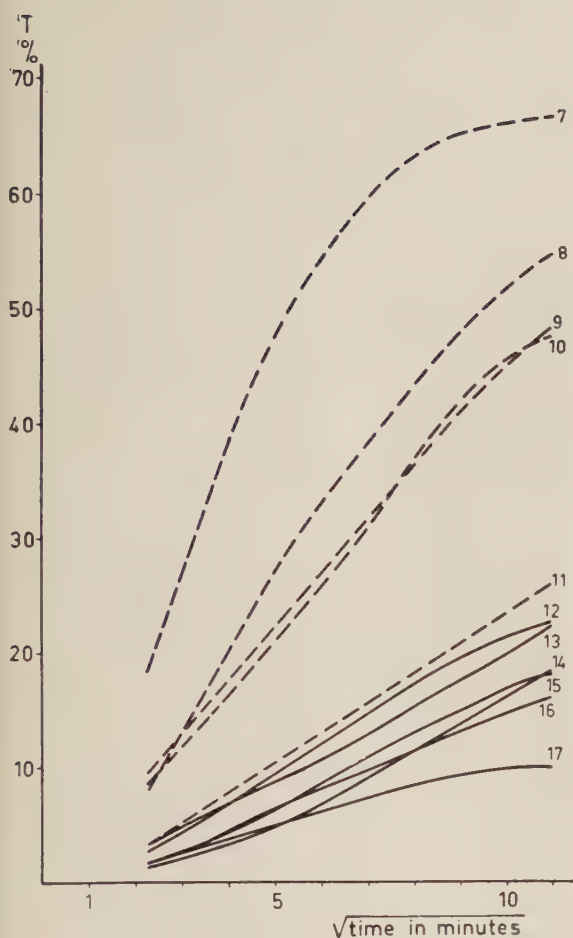


Fig. 54.

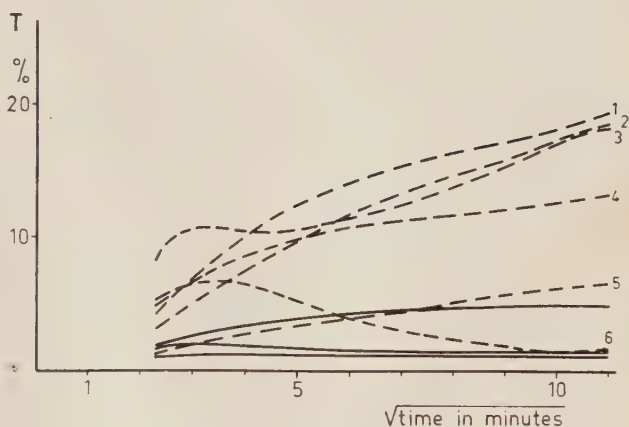


Fig. 55.

Figs. 54 and 55. Uptake curves in untreated (Fig. 54) and thiouracil treated (Fig. 55) subjects after intravenous injection. Broken curves: hyperthyroid subjects. Continuous curves: euthyroid controls.

a further two hours. Theoretically, a small part of the thyroid radioiodine will always be releasable as long as the blood contains inorganic radioiodide; when equilibrium has been reached between radioiodide in plasma and thyroid, the theoretically releasable amount will be equal to the product of the thyroid iodide space and the plasma concentration of radioiodide ($S \cdot P$). In untreated hyperthyroid subjects, S is high but due to the rapid accumulation of I^{131} in the gland P will be very low after 2 hours, so that

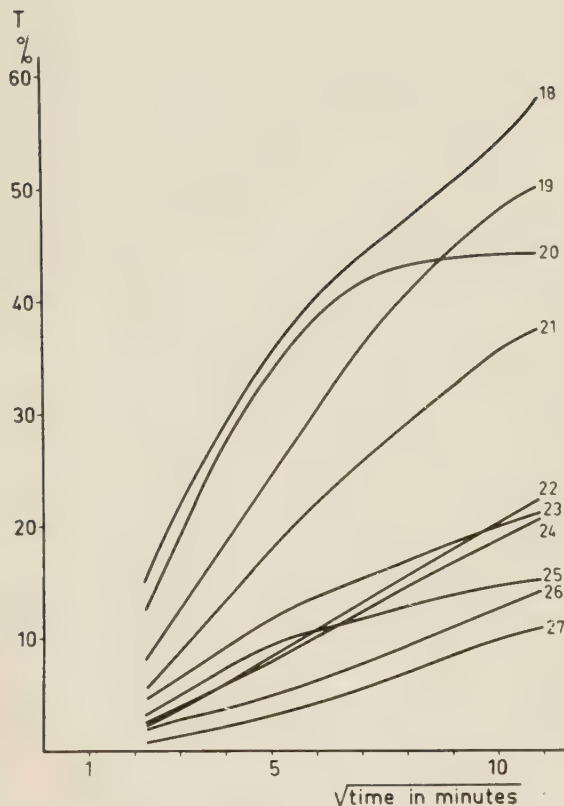


Fig. 56.

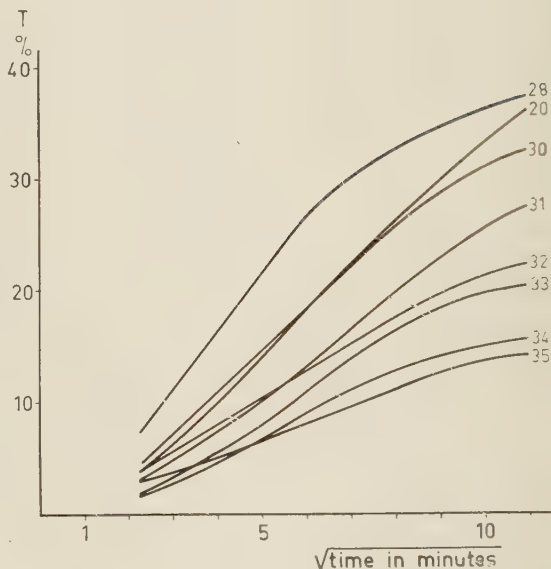


Fig. 57.

Figs. 56 and 57. Uptake curves in radioiodine treated subjects. Fig. 56: 2-4 months after treatment. Fig. 57: more than 6 months after treatment.

only an insignificant proportion of the thyroid radioiodine is inorganic and releasable. In euthyroid subjects, P is higher after 2 hours but S is rather low, so that here, too, no significant release after thiocyanate may be found. Fig. 58 illustrates the effect of thiocyanate in the untreated hyperthyroid and euthyroid subjects. There is a general flattening of the curves due to the inhibition of further uptake of I^{131} , but no significant release was found. Fig. 59 reveals the effect in the four thiouracil treated hyperthyroid subjects; in all cases there was a prompt release, starting within a few minutes after the administration. Figs 60 and 61 demonstrate the result in the radioiodine treated cases. In this respect, too, these patients generally behaved like the untreated subjects, *i.e.*, no significant amounts of thyroid I^{131} were released.

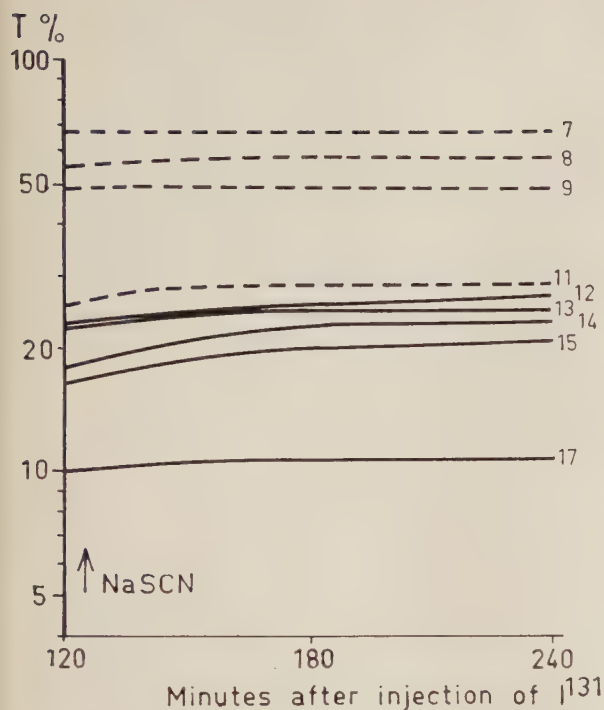


Fig. 58.

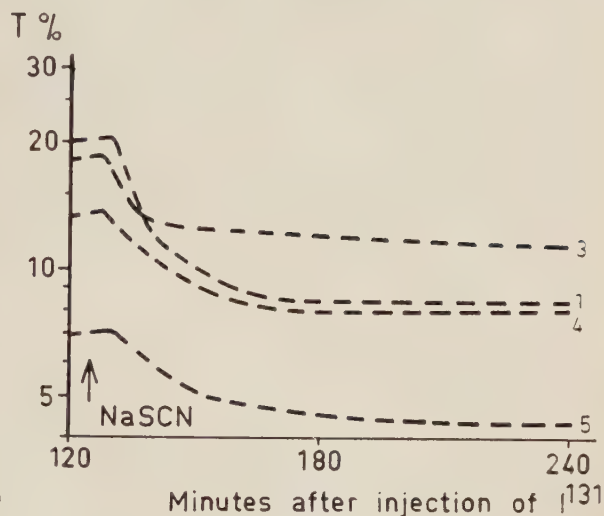


Fig. 59.

Figs. 58 and 59. Effect of 2 grams sodium thiocyanate on the thyroid radioiodine in untreated (Fig. 58) and thiouracil treated (Fig. 59) subjects. Broken curves: hyperthyroid subjects. Continuous curves: euthyroid controls. Logarithmic scale.

In one case (curve 25) a prompt, though rather slight release was observed; the thyroid uptake diminished from 15 to 12.5 per cent. In another case (18) there was a slow decrease from 59 to 50 per cent during the 2-hour period after thiocyanate administration. In no case, however, was there observed a release comparable with that in thiouracil treated hyperthyroid subjects or with that reported by *Kirkland* in radioiodine treated subjects.

The quotient between the rate of uptake in the gland and the plasma concentrations (thyroid clearance) was determined in respect of 10-minute intervals from 5 to 65 minutes. The results in untreated and thiouracil treated subjects are recorded in Table 4. In most of the untreated subjects the values were fairly constant throughout this period. Only one noteworthy exception was observed, a hyperthyroid patient (no. 7) in whom the values continuously dropped from 490 to 230 ml/minute during the investigated period. In this

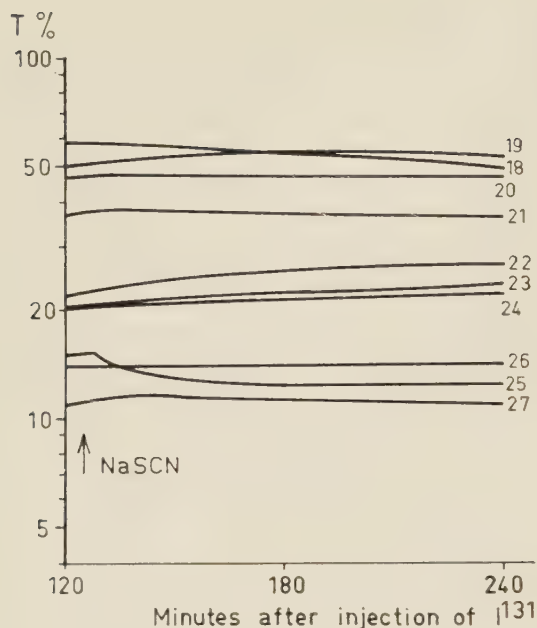


Fig. 60.

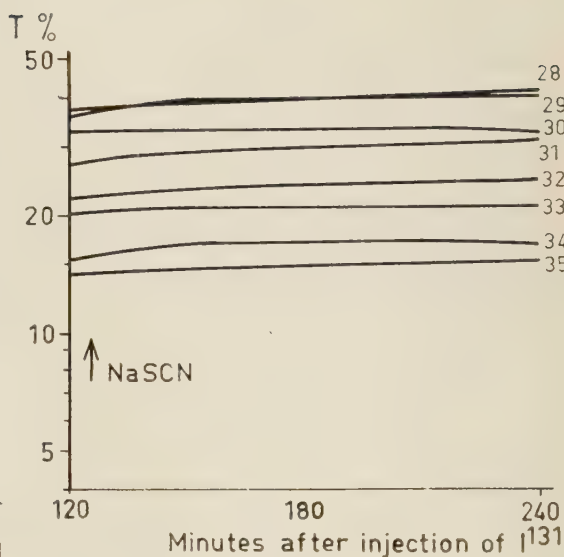


Fig. 61.

Figs. 60 and 61. Effect of 2 grams sodium thiocyanate in radioiodine treated subjects. Fig. 60: 2—4 months after treatment. Fig. 61: more than 6 months after treatment.

case the thyroid uptake curve had already approached its maximum after $1\frac{1}{2}$ hours (Fig. 54) and the inconsistency may be due to a rapid release of organic I^{131} from the gland; it may, however, also be due to the previously discussed back-diffusion of radioiodide from the thyroid to the blood (*Castenfors et al.* 50). From the practical point of view it is of interest to note that the average thyroid clearance values from 5—15 minutes and from 5—120 minutes in each individual untreated subject were fairly similar, and in none of the cases did the difference have any practical diagnostic importance (Table 4). In the thiouracil treated subjects, where the organic binding of iodine was impaired, rapidly decreasing values were observed during the early period, and sometimes even negative values (Table 4). The results in the radioiodine treated subjects are given in Table 5. Most cases behaved similarly to the untreated subjects, *i.e.*, the values were fairly constant throughout the investigated period, and it was of no practical importance whether the average thyroid clearance values were calculated from 5—15 or from 5—120 minutes. Four striking exceptions were, however, noted, in

which the thyroid clearance values showed a significant decrease during the first hour (nos. 25, 18, 23 and 28). It is worthy of note that two of these patients (25 and 18) were those in whom a slight, but significant release of I^{131} after thiocyanate intake was demonstrated. Three of these cases were examined about 2 months after I^{131} treatment (18, 23, 25) and the fourth after about 16 months (28).

Due to the complicated interrelation between plasma and thyroid radioiodine the conventional thyroid clearance cannot be regarded as a well-defined parameter of the thyroid function (*Castenfors et al.* 50). What from the functional point of view is of major interest to determine, is the rate at which the thyroid clears the plasma of stable iodide. Using the same symbols as those in formulae (5)–(10) in Chapter I, this rate (R liters/hour) may be expressed:

$$R = \frac{k_1 \cdot k_3}{(k_2 + k_3)} = S \cdot k_3 \quad \dots\dots\dots (11)$$

It would be most correct to call this expression the thyroid clearance. In order to avoid confusion with the conventional thyroid clearance, *Ingbar* (161, 162) introduced the term “thyroid iodide transfer rate”.

In Tables 4 and 5 the values found in this series for S , k_3 and R are tabulated.

The values were calculated according to the method of *Ingbar* described in Chapter I. In three thiouracil treated subjects, one hyperthyroid (6) and two euthyroid ones (36, 37), the thyroid curves indicated a very high degree of inhibition of the organic binding, and in these curves S was determined instead from the T/P ratio (*cf. Childs et al.* 60).

For S and k_3 two figures are given, one when the curve H_0B/B_0 was used as background correction and one when curve B was used; the last values in parentheses, as the first ones are likely to be the most correct.

For the radioiodine treated subjects the following symbols are used in Table 5 to signify their clinical state. *Re*: permanent remission. *Tr*: transient remission at the time of examination. *Im*: improved but still hyperthyroid.

As will be seen from Fig. 4, the untreated hyperthyroid subjects had high values for both S and k_3 . The untreated euthyroid controls had a smaller thyroid iodide space and usually also a lower k_3 value. The thiouracil treated subjects were all characterized by low values for k_3 , but a thyroid iodide space of the same order of magnitude as that in the untreated subjects. The

Table 4

		Hyperthyroid subjects													Euthyroid subjects																													
		Untreated													Thiouracil treated										Untreated										Thiouracil treated									
Case No.	7 EA (15.8)	8 AS (5.9)	9 EN (2.3)	10 KE	11 HA (2.0)	1 AG (3.2)	2 AG (2.3)	3 KE (4.2)	4 EF (2.3)	5 SJ (1.5)	6 KE	13 RR (1.3)	14 ET (1.5)	15 MK	16 KS (1.6)	17 AE (1.6)	36 HO (0.9)	37 BJ (0.6)	38 SL (1.3)																									
<i>S</i> liter	14.4 (15.8)	2.7 (5.9)	1.9 (2.3)	1.7	1.4 (2.0)	2.1 (3.2)	1.7 (2.3)	2.7 (4.2)	1.6 (2.3)	0.9 (1.5)	1.7	1.1 (1.3)	1.3 (1.5)	1.6	1.4 (1.6)	1.2 (1.6)	0.3 (0.9)	0.4 (0.6)	1.0 (1.3)																									
<i>k</i> ₃ fraction/hour	2.0 (1.8)	9.5 (4.4)	4.3 (3.6)	7.5	2.4 (1.6)	0.8 (0.4)	0.9 (0.8)	0.9 (0.6)	0.5 (0.4)	0.8 (0.5)	≥ 0	2.9 (2.6)	2.0 (1.7)	1.2	1.3 (1.4)	0.7 (0.6)	≥ 0	≥ 0	0.2 (0.1)																									
<i>R</i> ml/minute	480	430	132	215	53	26	26	40	12	12	≥ 0	50	44	32	32	15	≥ 0	≥ 0	3.5																									
5-15 minutes	486	390	103	148	61	64	47	48	41	21	34	55	31	31	41	33	0.9	1.2	22																									
15-25 "	417	390	106	151	52	42	41	2	20	18	2.5	42	29	33	46	30	1.2	-1.6	12																									
25-35 "	352	357	103	159	55	34	29	23	11	13	-8.5	43	56	34	38	24	1.2	-1	6																									
35-45 "	330	318	119	166	54	21	29	27	11	12	-13	50	42	35	44	23	0	-1	4.5																									
45-55 "	280	310	115	160	45	16	27	30	6	11	-14	43	45	35	52	20	0	-0.5	2.5																									
55-65 "	230	306	118	173	51	19	22	30	6	8.5	-14	55	56	35	58	23	0	0	2.5																									
5-120 minutes	342	348	103	166	52	29	30	29	15	13	-11	49	42	33	48	20	0.4	0.4	5.8																									
Thyroid clearance ml/min.																																												

Thyroid clearance ml/min.

Table 5

	Radioiodine treated subjects																		
	2-4 months										> 6 months								
	18	19	21	23	25	24	26	27	22	28	29	30	31	32	33	34	35		
Case No.	GE	HK	AS	EB	SW	VD	HG	AJ	IL	MJ	BN	VSH	VH	AL	GS	EN	KL		
Time after treatment Months	2	2	2	2	2	4	2	2	4	16	16	7	17	7	24	30	13		
Clinical state	Im	Im	Tr	Tr	Im	Re	Re	Re	Re	Re	Re	Re	Re	Im	Re	Re	Re		
S liter	7.5 (8.9)	4.7 (7.4)	4.1 (5.0)	3.2 (3.6)	1.9 (2.1)	0.6 (1.2)	0.4 (0.6)	0.7 (0.7)	1.4 (1.7)	6.9 (9.0)	2.9 (4.8)	2.7 (3.7)	0.9 (1.2)	1.9 (3.0)	2.2 (2.8)	1.5 (1.4)	1.2 (1.3)		
k_3 fraction/hour	1.7 (1.4)	1.9 (1.1)	1.7 (1.4)	0.9 (0.8)	0.7 (0.8)	6.0 (2.3)	3.2 (2.0)	2.0 (1.9)	1.9 (1.8)	0.6 (0.4)	2.4 (1.8)	2.2 (1.7)	2.7 (2.0)	1.1 (0.8)	1.0 (0.9)	1.0 (1.1)	1.3 (1.2)		
R ml/minute	210	146	114	45	22	45	19	22	45	66	113	100	39	35	38	24	26		
5-15 minutes	169	154	107	79	47	39	16	19	38	106	85	102	37	47	44	35	25		
15-25 "	146	148	91	60	34	38	14	23	44	111	85	98	36	47	49	33	22		
25-35 "	130	148	99	45	24	39	18	21	48	97	101	97	40	49	58	34	25		
35-45 "	119	146	91	39	17	41	22	27	50	73	100	102	37	35	65	38	26		
45-55 "	121	114	86	44	17	37	23	26	53	69	103	110	44	45	72	30	28		
55-65 "	118	130	97	38	15	39	18	27	53	60	96	103	42	31	46	34	20		
5-120 minutes	135	129	95	48	23	38	19	24	45	77	87	94	37	37	47	28	20		
Thyroid clearance ml/min.																			

findings in this respect agree with those reported by *Ingbar* (161, 162). The condition in the radioiodine treated subjects was not uniform. The series contains a few cases with a strikingly large thyroid iodide space and a low rate constant for organic binding (cases 25, 23 and 28); in all these cases there was also a pronounced decrease in the thyroid clearance values throughout the investigated period. Two of them were examined 2 months after radioiodine treatment (25, 23) and both showed, at that time, only a transient improvement or transient remission. The third case (28), however, where the discrepancy was especially large, was examined after 16 months and had a clinically demonstrable remission. Yet the series also includes examples of the opposite kind; namely, a small thyroid iodide space and a very high degree of organic binding (Cases 24, 26, 27, 31); in all these cases the thyroid clearance values were constant throughout the period. All of these patients had full clinical remissions.

Three cases were selected for the investigation due to a strikingly rapid accumulation of I^{131} in the gland despite clinical euthyroidism (28, 29, 30). In two of them (29, 30), both S and k_3 showed high values and the thyroid clearance values were fairly constant during the first hour. In these cases impaired organic binding with retained ability to concentrate iodide can hardly be the explanation of the discrepancy between the clinical picture and the tracer test. The third of the cases (28) was the one previously described with a very large thyroid iodide space and a low k_3 value. This case probably had highly impaired organic binding but still a good capacity to concentrate iodide. The early deviation from a linear course, when the uptake was plotted against the square root of time (Fig. 57), may be a manifestation of the same mechanism, and also the falling thyroid clearance values. It is difficult to explain, however, why a release was not obtained with thiocyanate. The thyroid uptake after two hours was 37 per cent and the plasma concentration 2.25 per cent per liter. With a thyroid iodide space of 6.9 liters, 16 per cent of the given dose of I^{131} could be expected to have been in inorganic form in the thyroid and releasable with thiocyanate. It is probable that the blood concentrations of thiocyanate were not sufficient; but in the thiouracil treated subjects, where the same technique was used, there was good agreement throughout between the released amount of I^{131} and the $S \cdot P$ quotient.

Of practical interest is the close agreement between the $S \cdot k_3$ quotient and the thyroid clearance values in all cases where the latter values were fairly constant. In the other untreated or radioiodine treated subjects, too, the

difference between $S \cdot k_3$ and the average thyroid clearance values during the first 2 hours was not too large to be ignored from the practical diagnostic point of view.

The above investigation is the most detailed of its kind that has been reported in radioiodine treated subjects. Nevertheless, for several reasons it does not justify any far-reaching conclusions. The series is rather small and the variations are large. *Wijnblad* suggested, in a discussion, that in this respect there may be differences due to the type of goiter, for instance depending upon the vascularization. Such variations are very likely. *Ingbar* studied a large number of euthyroid controls and hyperthyroid subjects. In the normal subjects the findings were fairly uniform, but in the toxic goiters the condition varied considerably; some cases had, for instance, a very large thyroid iodide space and a moderate degree of organic binding; others a smaller iodide space but a very high binding rate. If the variations in untreated goiters are large, even greater variations may be expected in radioiodine treated subjects. Some patients have, after the treatment, a substantially reduced mass of thyroid tissue, and even if the thyroid/plasma gradient is greatly increased the total thyroid iodide space will be low. If such a gland is still to be capable of utilising an amount of iodine sufficient for adequate hormone production, the iodide in the thyroid will have to be converted to organic form at a very high rate. On the other hand there may be stages after the treatment when the mass of functioning thyroid tissue is still abnormally large but the function of the thyroid cells is partially inhibited due to the irradiation reaction. During such a stage a large thyroid iodide space but a low rate of organic binding may possibly occur. Due to these variations, an investigation of the foregoing kind, to be conclusive, would probably have to comprise a large number of untreated and treated subjects or be repeated several times in individual patients before and after treatment.

Other objections may be raised concerning the validity of the methods used, *i.e.*, accumulation gradient, release of I^{131} after thiocyanate, constancy of the thyroid clearance values and numerical calculation of S and k_3 . With the methods at present available it does not seem possible, however, to elucidate the problem more fully in a clinical series. As regards the mathematical calculation of S and k_3 , definite simplifications (*Ingbar*) have been made. Further investigations may perhaps show that these approximations are not justified. One of the postulates is that the release of organic I^{131} from the thyroid may be ignored. This assumption has usually been made for

similar calculations during the "iodide phase", and has been vindicated by the observation that protein-bound I^{131} in the plasma appears very slowly after the administration. Recent observations have, however, revealed that tri-iodothyronine may be given to patients with myxedema in pharmacologically adequate doses without an increase in the SPI values, and also that it is very rapidly metabolized, with liberation of inorganic iodide. Release of labelled tri-iodothyronine from the thyroid cannot, therefore, be expected to increase the PBI^{131} values, and if this transfer occurs rapidly it should definitely change the picture and render invalid most mathematical analyses hitherto used for the accumulation phase of I^{131} in the gland.

Despite these objections, the author has reported this investigation. It gives, in several respects, a more differentiated picture of the problem than does *Kirkland's* report, and it does not support the view that selective impairment of the organic binding of I^{131} in the gland is consistently or commonly found during an early phase after radioiodine treatment.

There are also, of course, other possibilities of selective or qualitative changes in the iodine metabolism after radioiodine treatment, and it is conceivable that detailed analysis of the iodine metabolism, using quantitative methods with parallel estimations of I^{131} and I^{127} and qualitative methods with analysis of different I^{131} fractions in blood or in excised thyroid tissue, would reveal information of interest. On the whole, and having regard to other known effects of irradiation it seems most likely, however, that radioiodine treatment is a non-selective, destructive form of treatment insofar as the thyroid tissue is concerned, and that in this respect it is analogous with surgical treatment.

5. The Release of Organic I^{131} from the Gland

As discussed in Chapter I, the release of organic I^{131} from the gland is often rapid in patients with remissions after surgical and radiological treatment. Tests based on this phase of the I^{131} metabolism will often give values of the same type as that observed in untreated hyperthyroid subjects (*Freedberg et al.* 91, 92; *Horst et al.* 153, 155, 157; *Ansell et al.* 9).

The only detailed study to be reported concerning the behaviour of PBI^{131} and the biologic half-life of I^{131} in the gland after radioiodine treatment of hyperthyroidism, was conducted by *Horst*. He found that most patients, despite euthyroidism revealed by clinical data and other laboratory tests, had

a pathologically short biologic half-life of I^{131} in the gland and increased PBI^{131} values.

In this series estimation of PBI^{131} after 48 hours was performed in 86 cases with clinical euthyroidism observed from 9 months to 3 years after the treatment. All patients visiting the hospital during one period were, wherever possible, examined in this way, and the series may thus be regarded as unselected. In 70 of these cases, SPI was also estimated. The results are illustrated in Fig. 62. The SPI values had a fairly normal distribution, with a mean of $5.9 \mu g$ per cent and 8.7 as the highest value noted. The PBI^{131} had a very wide range from undetectable quantities up to 4.6 per cent per liter, with an average of 0.93 per cent per liter. If the upper normal limit is arbitrarily set as high as 0.5 per cent per liter, 59 of the 86 cases had pathologically high values. There was, as could be expected, no correlation between SPI and PBI^{131} . PBI^{131} after 48 hours was also determined in 42 euthyroid controls with an average value of 0.18 per cent per liter, all values falling below 0.5 per cent per liter. Due to the technique used, the estimates in the low range were greatly influenced by random errors of measurement; but this does not affect the conclusion that the majority of the treated patients had pathologically increased values.

In 70 of these patients (III), in the 42 euthyroid controls (II), and in a consecutive series of 23 cases with untreated hyperthyroidism (I), the release of I^{131} was also studied by repeated measurement over the thyroid. The average values obtained are illustrated in Fig. 63, plotted on a logarithmic scale. The disappearance rate of I^{131} from the gland was much greater in the radioiodine treated subjects than in the euthyroid controls, the biologic half-life for the average curve from 2—8 days being about 9 days compared with about 50 days in the controls. If the series was divided into cases with PBI^{131} values below 0.5 per cent per liter (III a, 19 cases) and above 0.5 per cent per liter (III b, 51 cases), both groups had an increased disappearance rate of I^{131} in the gland, with an average BHL of about 12 days in the former and of about 8 days in the latter. The difference was accordingly rather small in this respect. The former group had, however, an average 3 hours uptake of only 16.7 per cent compared with 25.6 per cent in the latter group; and a probable contributory cause of the difference in PBI^{131} values in these two groups was the difference in the uptake. It would thus seem that extremely few radioiodine treated subjects really have a normal release of organic I^{131} from the thyroid. The explanation of this mechanism is, in all probability, a reduced

Patients with remission of
hyperthyroidism after radioiodine
treatment.

PBI¹³¹ after 48 hours

%/liter



SPI

μ/100 cc



Fig. 62.

Thyroid uptake

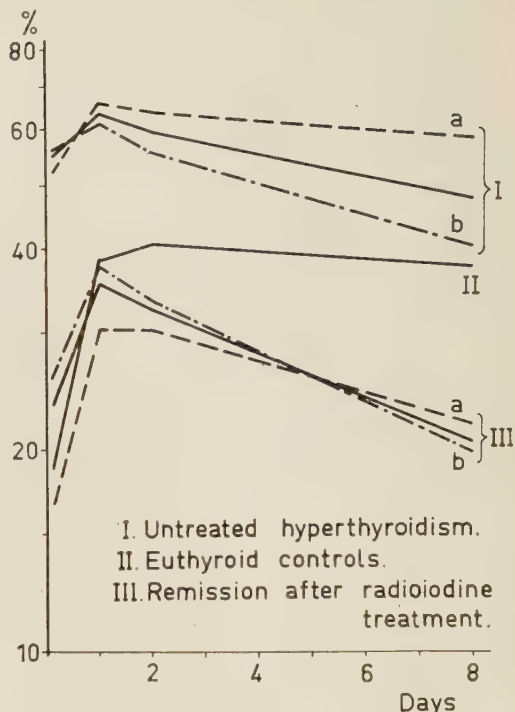


Fig. 63.

Fig. 62. PBI¹³¹ and SPI in patients clinically euthyroid after radioiodine treatment. Black circles represent cases in which both examinations were performed.

Fig. 63. Average values for 3 hours, 1 day, 2 days and 8 days gland uptake in 23 cases with untreated hyperthyroidism (I), 32 euthyroid controls (II), and 70 patients euthyroid after I¹³¹ treatment. *a*. Average curves for patients with PBI¹³¹ after 48 hours below 0.5 per cent. *b*. Average curves for patients with PBI¹³¹ after 48 hours above 0.5 per cent.

thyroid hormonal iodine pool, necessitating a higher rate of transfer in order to ensure adequate hormone secretion.

High PBI¹³¹ values have also been reported in cases with postsurgical hypothyroidism (*Blom et al.* 35). Most cases with hypothyroidism in this series had so low an uptake that high values of PBI¹³¹ could not be expected. In one case with clinically demonstrable hypothyroidism despite a normal 24 hours uptake (30 per cent), PBI¹³¹ was determined after 48 hours and was 0.8 per cent per liter; that is, increased despite the hypothyroidism.

This rapid release of organic I¹³¹ from the gland undoubtedly influences the 24 hours uptake in many cases. As will be seen from Fig. 63, the average 3

hours uptake was higher in the patients with remissions after radioiodine treatment than in the euthyroid controls, but the 24 hours uptake was slightly lower in the former — certainly an expression of this mechanism. As shown in Figs. 37 and 38, the sum of T_{24} and U_{24} was throughout somewhat lower in the treated subjects than in the controls, probably also for the same reason. This influence on the 24 hours uptake is, in the majority of cases, of no great practical importance. For a small group of patients with extremely rapid turnover of organic I^{131} from the gland it will, however, cause a striking discrepancy between the 3 hours uptake and the 24 hours uptake and also between the latter and the 24 hours urinary excretion. In some cases of that type, this characteristic was strikingly constant throughout the course and both before and after treatment. The patient with the highest PBI^{131} value noted in this series was examined a total of six times during a 2 years period, both before and after which a remission had been induced; at each examination she had PBI^{131} values of 4—6 per cent per liter and an extremely short BHL of I^{131} in the gland. A simple adjustment of the therapeutic activity to the size of the gland is, in such cases, definitely unsatisfactory and will lead to pronounced underdosage. Even if a simple and more convenient dosimetry is used in the majority of cases, a more detailed average dose calculation will always be indicated in these cases. If T_{24} and U_{24} are used as standard tracer tests, a rapid disappearance rate of I^{131} may be suspected in all cases where U_{24} is low but T_{24} is not increased to a corresponding degree.

Summary

The present investigation had two principal aims: to analyze the results of radioiodine treatment in a series of hyperthyroid subjects treated from 1951 to 1953 at Radiumhemmet and to analyze the behaviour of the radioiodine tracer tests after the treatment.

In Chapter I a survey of the tracer tests with radioiodine is given. The physiologic principles for different tests dealing with the accumulation phase of I^{131} in the gland and the release of organic I^{131} are discussed in connection with a review of the literature and with special reference to the tests used in the present series. The measuring technique used is described. A method, introduced at the laboratory, which makes it possible to use the changes in the counting rates measured over the neck during the first few minutes after intravenous injection of I^{131} as an index of the thyroid function, is discussed, and a new principle for correction of "body background" during this initial phase is described. A general scheme of the investigation is given at the end of the Chapter.

In Chapter II the principles of radioiodine treatment and factors of importance to the results are discussed in conjunction with a survey of the literature. In the years 1951 to 1953, 370 patients with hyperthyroidism were treated at Radiumhemmet, 202 of them selected for the treatment at the Goiter Department of St. Göran's Hospital. Most of them were treated on special indications (advanced age, complicating diseases, recurrent hyperthyroidism after subtotal thyroidectomy, poor response to preoperative treatment, small goiters, etc.); 361 of them were available for analysis of the therapeutic results and were followed up until the end of 1954 or the beginning of 1955. The composition of the series is analyzed with respect to age, sex, complications, previous treatment, and type of goiter. A simple technique was used for the treatment, mainly with adjustment of the administered therapeutic I^{131} activity to the size of the goiter and re-treatment after about 2 months if the patient was still clinically hyperthyroid and had a tracer test

of hyperthyroid type. The end results in the total series and in the different types of toxic goiters, and also the results up to different times from the start of treatment, are reported. They show that radioiodine may, in most cases and regardless of the type of goiter, bring about a remission; in some cases, however, only after several treatments. About 12 per cent of the cases were still hyperthyroid one year after the start of treatment, but only about 1 per cent two years after its start. The incidence of permanent hyperthyroidism was 13 per cent. It was highest in the groups with recurrent hyperthyroidism after thyroidectomy and primary hyperthyroidism without demonstrable goiter, probably due to overdosage. It could be demonstrated that the incidence of hypothyroidism was greatly reduced with increasing experience of the management of these cases. The risk of exacerbation of hyperthyroidism during the initial period after the treatment is discussed and two patients with cardiac complications, in whom such exacerbations were probably a contributory cause of death, are reported. Case histories are presented for a series of illustrative cases.

In Chapter III the behaviour of the radioiodine tracer tests before and after treatment is described. In cases with a good clinical response the ability of the gland to accumulate I^{131} was often depressed to a sub-normal level during the first few months after treatment, followed by a "recovery" during the following months. The changes in the tracer tests usually proceeded more rapidly than the changes in the clinical picture, and early tracer tests therefore gave information of considerable prognostic value both as regards the chance of definite remission after a single treatment and as regards the risk of permanent hyperthyroidism. After some months the accumulation of I^{131} in the gland returned to a normal level, with a distribution very similar to that in euthyroid controls; this was revealed by both the 3 and the 24 hours uptake and by initial registration of the thyroid uptake curves after intravenous injection of the tracer dose. In a small group of patients there was a tendency to elevated accumulation of I^{131} when the initial depression of the function had been passed and despite clinical euthyroidism; tests of extreme hyperthyroid type as in some untreated subjects were, however, not observed. With the treatment technique used, moreover, there was a striking correlation between the 24-hours urinary excretion of I^{131} before the treatment and the clinical result after a single treatment. The chance of definite remission was about 2—3 times greater when the excretion exceeded 30 per cent than when it was below 10 per cent. The cause of this correlation

is discussed, and the most probable explanation is that cases with a low urinary excretion also have, on the average, a rapid release of hormonal I^{131} from the gland and therefore receive smaller irradiation doses when the therapeutic activity is adjusted only to the size of the gland.

In one part of the series a detailed study was made of the organic binding of I^{131} in the gland in radioiodine treated subjects, using partly the releasability of the thyroid I^{131} with thiocyanate and partly the interrelation between the thyroid uptake curves and the plasma concentration curves during the first 2 hours after intravenous injection of I^{131} . The results did not support the view that inhibition of organic binding of iodine with retained iodide concentrating capacity is a constant or important mechanism in these cases.

In the last part of Chapter III a study of the release of organic I^{131} is reported in cases with clinical remissions after prolonged observation. The investigation confirms that the release of organic I^{131} is usually pathologically increased in these cases despite clinical euthyroidism, probably due to a reduced hormonal iodine pool. These cases had a normal distribution of the values for stable protein-bound iodine in the serum. Tests based on the release of organic I^{131} from the gland are thus definitely unsuitable as a means of studying the thyroid function after radioiodine treatment.

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Price Sw. Kr. 25:—